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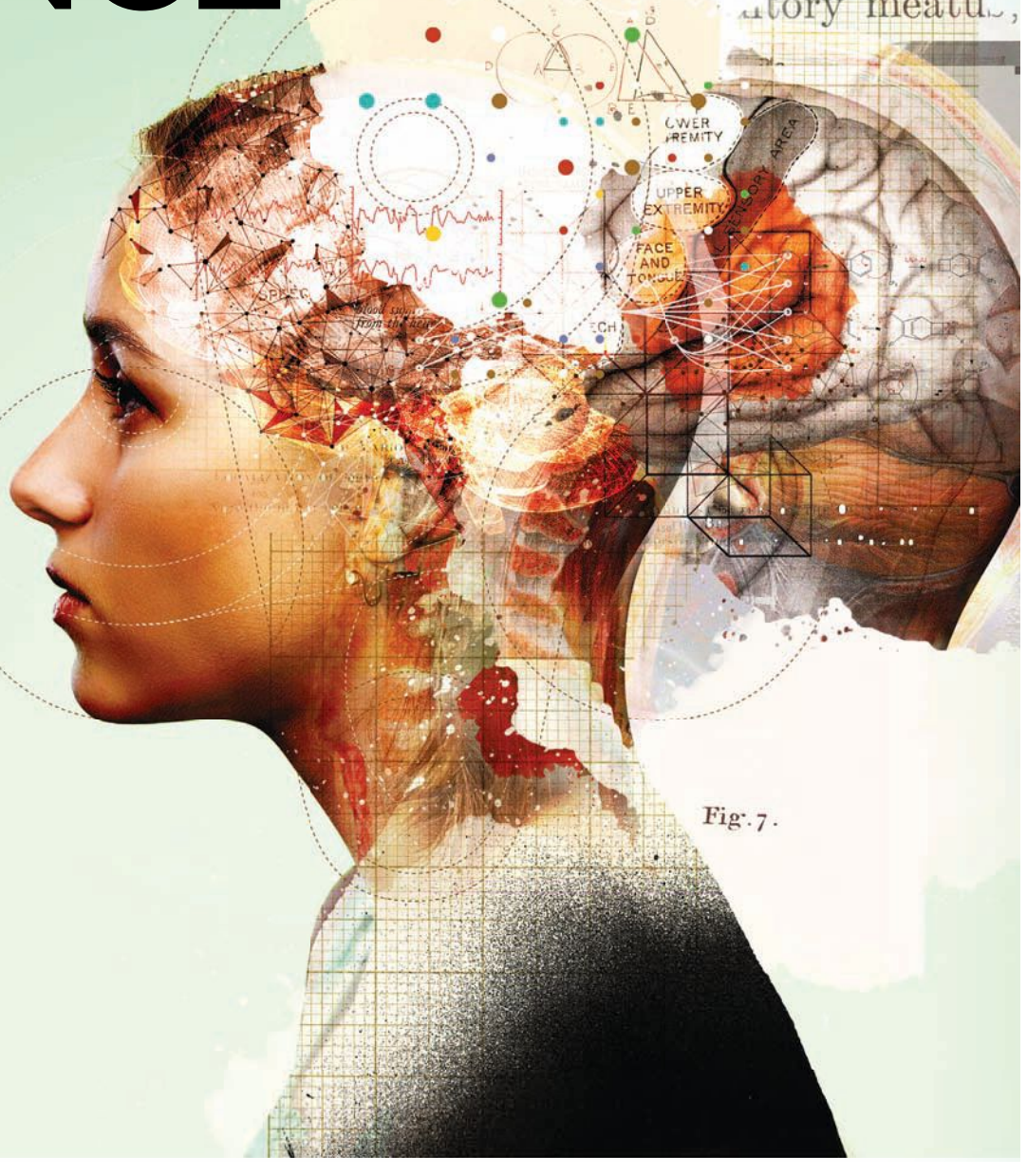

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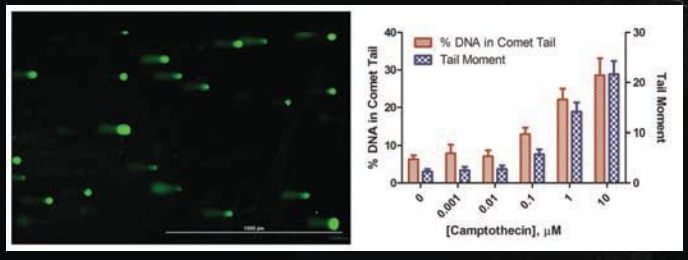

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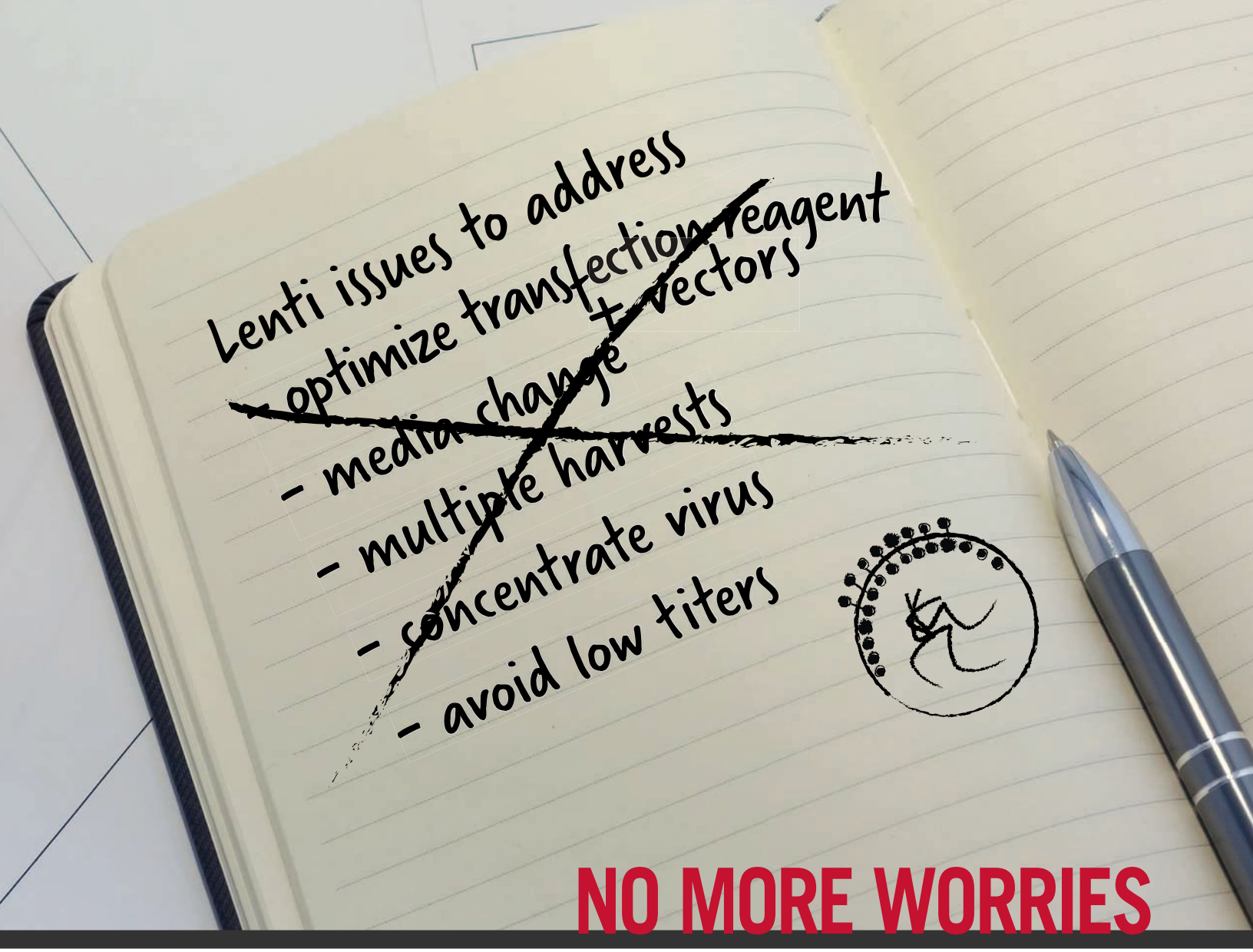

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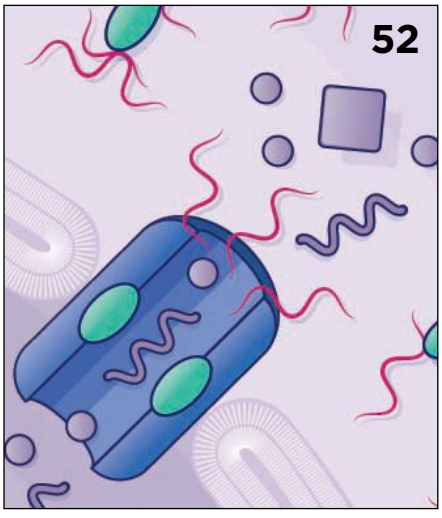

MOUNT SINAI HEALTH SYSTEM; © TAMI TOLPA; © RICHARD BOLL

CORRECTIONS:
The October 2018 article "Data Rush" incorrectly stated that Luna DNA will compensate users in cryptocurrency. They will be compensated with shares of the company. *The Scientist* regrets the error.

PUZZLE ON PAGE 14

B	L	O	W	H	O	L	E	■	H	E	R	B
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K	■	U	■	■	■	Z	■	I	■	■	■	I
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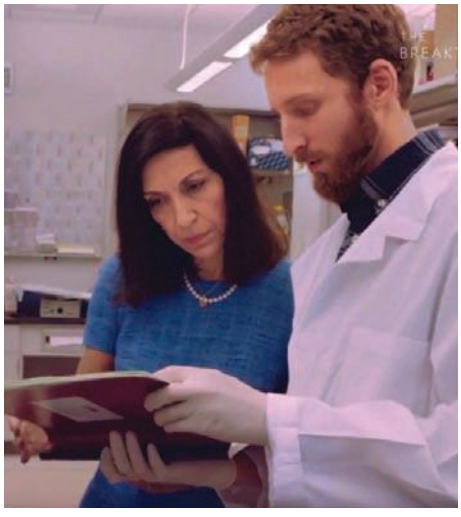


THIS MONTH AT THE-SCIENTIST.COM:

VIDEO
Global Virus Doc
Author and researcher Peter Hotez explains the campaign to combat neglected tropical diseases.

VIDEO
Award Winner
Geneticist and profilee Hoda Zoghbi describes her work on rare diseases.

VIDEO
The Human Whisperer
Meet Joey Ramp, a University of Illinois neuroscience student who is fighting to continue her education with her service dog by her side.

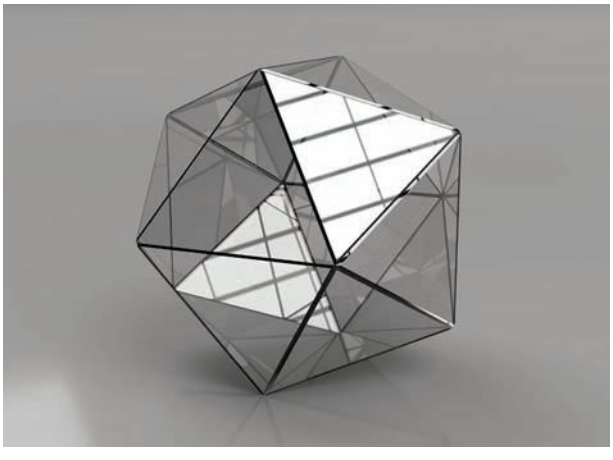
AS ALWAYS, FIND BREAKING NEWS EVERY DAY ON OUR WEBSITE.

Coming in December

HERE'S WHAT YOU'LL FIND IN NEXT MONTH'S ISSUE

- The science behind microcompartments within cells
- Membraneless organelles come into focus
- This year's Top 10 Innovations
- The dynamic role of fat cells in lactation

AND MUCH MORE



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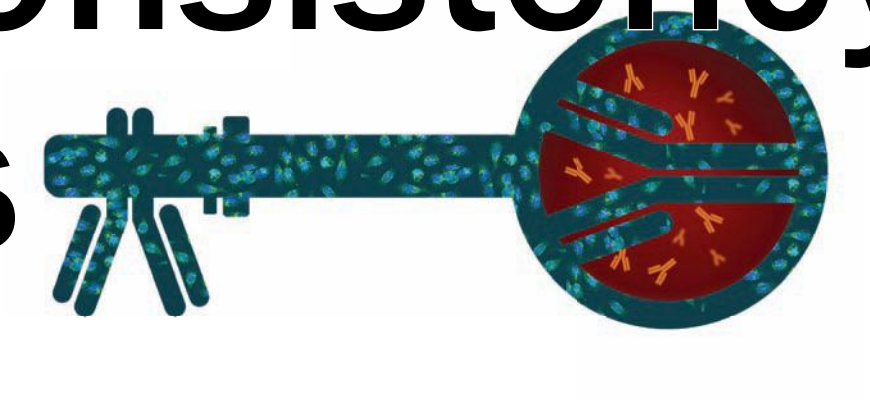

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Contributors

Emily Cox and **Henry Rathvon** are sexagenarians (a word that starts well but finishes a bit anticlimactically) who merged minds and hearts on the campus of Tufts University in the 1970s.

He majored in English, while she studied electrical engineering; they both had a bent (or was it a warp?) for wordplay. Puzzle-writing followed as naturally as a falling piano follows the laws of gravity.

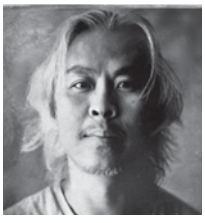
Residing now in Lemoyne, Pennsylvania, near the Susquehanna River, they make puzzles for the *Boston Globe* (Sunday crosswords), the *New York Times* (biweekly acrostics), the *Wall Street Journal* (cryptic crosswords), and *Readers Digest* (vocabulary quizzes).

Their puzzles for *The Scientist* are (like this biographical blurb) pangrammatic (i.e., they use every letter of the alphabet). Check out their latest puzzle on page 14. (*Written by the wordsmiths themselves.*)

Peter Hotez was captivated by maps and microorganisms as a child. "I think tropical diseases became the natural hybrid of maps and global awareness and microbial disease," says Hotez, who is the Dean for the National School of Tropical Medicine at Baylor College of Medicine in Houston, Texas, and develops vaccines for poverty-related tropical infections. He grew interested in vaccines while working on his doctoral and medical degrees, which he earned from Rockefeller University in 1986 and Weill Cornell Medical College in 1987, respectively. As an MD/PhD student, he began crafting a vaccine to tackle human hookworm infection, which strikes several hundred million people globally.

Along with being a PI, Hotez considers himself a science advocate, urging parents to vaccinate their children. An author of three books, Hotez's most recent, *Vaccines Did Not Cause Rachel's Autism*, addresses the fallacies surrounding vaccination's role in causing autism, through the prism of his own family's experience with the disorder. "The fact that I'm both a vaccine scientist, a pediatrician as well as an autism dad . . . I found myself in a unique position to be able to counter this aggressive and well-organized anti-vaccine movement."

Hotez writes about his book, his work, and his life on page 66.



Graphic artist **Dung Hoang** calls his creative process "furious," a description reflected in the name of his Salt Lake City, Utah, studio—Furious Visual World. The end result of this process evokes not anger, but a sense of dreaminess, an ethereal, dynamic world of science and fantasy, as evident on the cover of this month's issue.

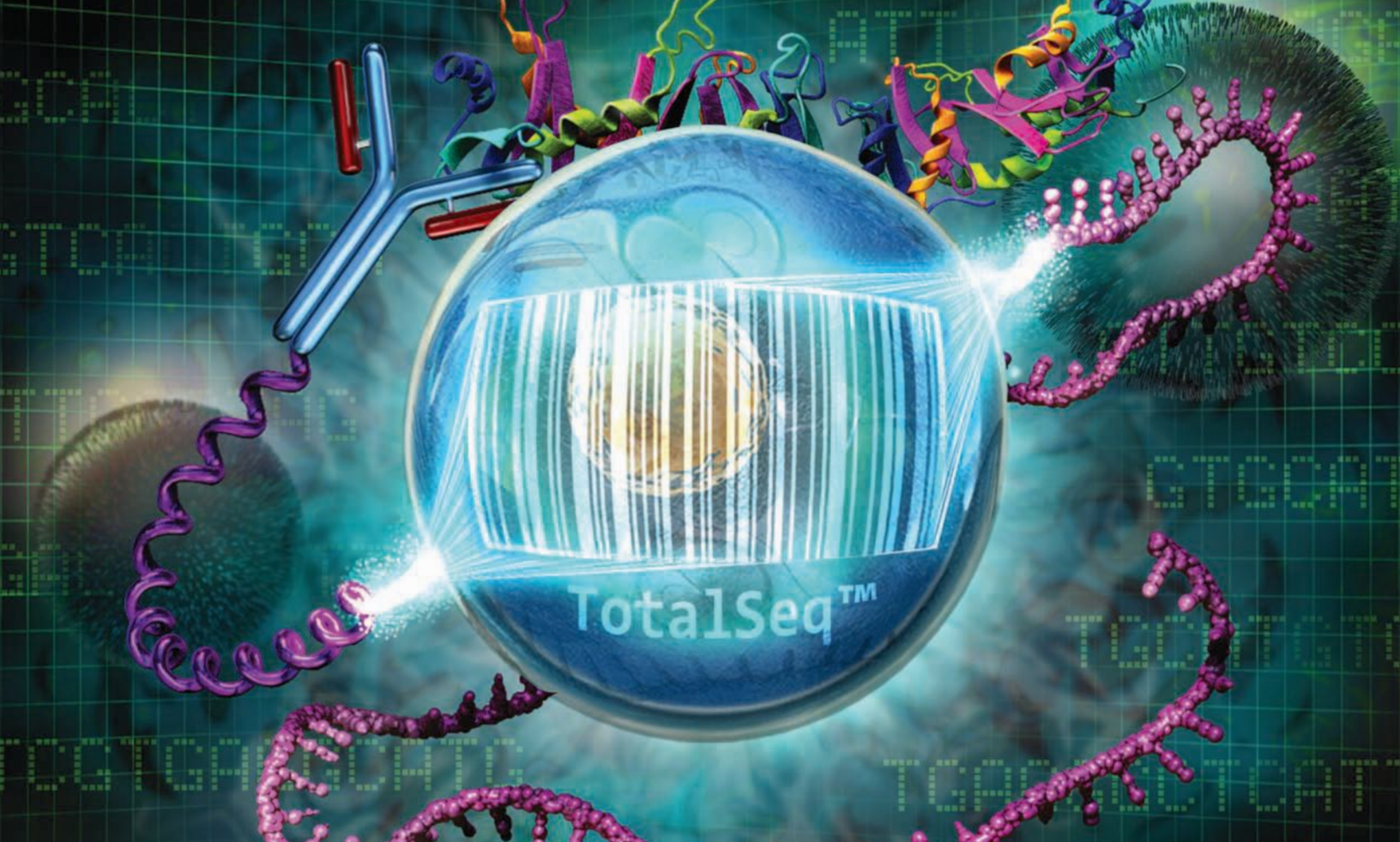
A native of South Vietnam, Hoang and his family fled the war-torn country when Saigon was captured by the Viet Cong in 1975. Dodging a hail of gunfire, the family was led by Hoang's naval officer father to a waiting vessel that would eventually carry them to safety. "We got out on a fishing boat, drifted out to sea for a few days, and later we were picked up by an aircraft carrier," Hoang recalls.

After immigrating to the US, Hoang's parents expected him to pursue a conventional career. "Because of my Asian upbringing, my parents really wanted me to be a doctor," he says. "I was really groomed for that."

But after majoring in prepharmacy and premed as an undergrad, Hoang decided that his childhood doodling more accurately reflected his true passions. "I just realized that I was making a big mistake," he notes. "I didn't want to be wearing a white lab coat."

Although he went on to pursue art, Hoang's work shows hints of his scientific chops. For this month's cover, he created an image that feels like a frenetic cross between photo montage, collage, and daguerreotype to illustrate the concept of science's hunt for the biological roots of intelligence. "I try to be as spontaneous as possible," Hoang says. "The illustrations are so layered that whether you look at it now or later, hopefully you discover a new thing."

COURTESY OF EMILY COX AND HENRY RATHVON; BRIAN GOLDMAN



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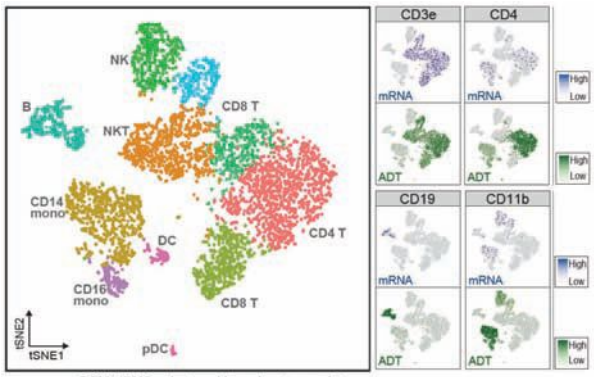

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Smarts and Hearts

IQ can't capture the breadth, depth, or variety of human intelligence.

BY BOB GRANT

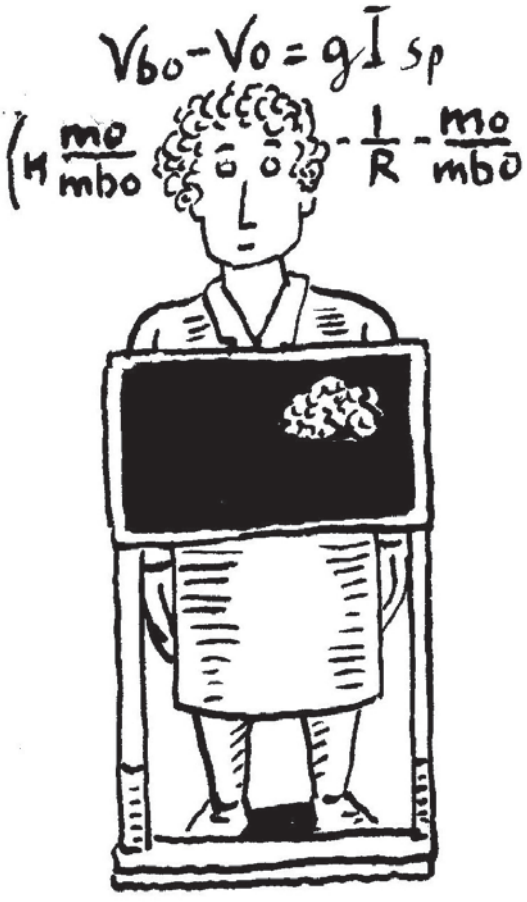
Often human intelligence is presented as a broad abstraction, a somewhat amorphous concept that may or may not be grasped by the pointed calipers of science. Is there a genetic component? Do proxies of intelligence—such as IQ tests—really capture the phenomenon? Might there be a way to increase intelligence once we have a firm understanding of its biological roots?

Associate Editor Shawna Williams deftly tackles these big-picture questions in her feature story, "The Intelligence Puzzle," on page 28. She talks to scientists at the forefront of intelligence research, and poses this intriguing question to readers: "Is our species smart enough to understand the basis of our own intelligence?"

I personally think humans are up to this ambitious neuroscientific challenge. But I've recently been mulling over some less-ballyhooed manifestations of intelligence. I do think there is utility in dissecting general intelligence and thinking about its component biological, environmental, and social drivers. But I also think that intelligence blossoms in more-subtle ways that are too often overshadowed by the IQ-testable variety.

Firstly, specialized knowledge has played a pervasive part in human economies and societies for millennia. As our species transitioned out of hunting and gathering and began to settle into a more sedentary lifestyle, carving off a specific slice of the human intelligence pie became valuable. Scribes, wheel makers, boat builders, and bakers could not only trade on their acquired knowledge and skills, they were afforded special status in their communities. That segmenting of human intelligence continues to this day, as journalists, home builders, and teachers make livings from having specific types of intelligence and skills that are not widespread across the population.

Beyond this economically vital segmenting of human intelligence, traits such as honesty, kindness, and civility are born of an even more fundamental intelligence, something that is missed by IQ tests. In a world too often beset by obfuscation, rudeness, and confrontation, these nobler attributes might be construed as weakness. But such behavior is a strength, capable of making society more inviting, inclusive, and peaceful. Although being dishonest, for example, might net a human short-term gains, the breakdown of factuality and honesty weakens the very fabric that binds together our institutions and our civilization.



ANDRZEJ KRAUZE

When human intelligence is parsed into its pragmatic parts, it begins to look less like a uniform quality that each of us possesses to a greater or lesser extent and more like a diverse human trait with a spectrum of variants. Sure, we need brilliant people exercising their cerebral cortices in order to explore space, combat disease, and increase our understanding of the laws that govern our universe. We also need pilots, lawyers, and roofers. But if attaining lofty intellectual heights or maintaining specialized knowledge and skill sets is not paired with progress and thoughtfulness in the ways humans treat each other and our planet, it makes our species seem, ultimately, kind of dumb. ■

Editor-in-Chief
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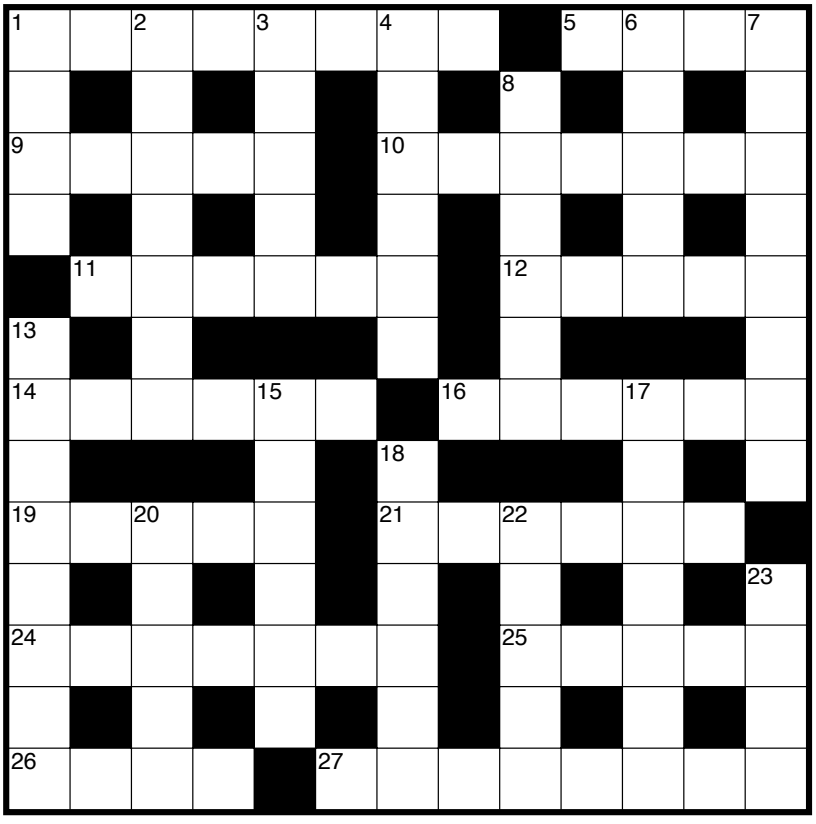
Speaking of Science



Note: The answer grid will include every letter of the alphabet.

BY EMILY COX AND HENRY RATHVON

ACROSS

1. Nostril in the top of 1-Down's head
5. Parsley, sage, rosemary, or thyme
9. Opposite of general, to anesthesiologists
10. Red plant stalk, or donnybrook
11. Anatomical source of ill humor?
12. Douglas Hofstadter's ___, *Escher, Bach*
14. Exam on which a normal score is about 100 (2 wds.)
16. Falcon, or sorcerer of legend
19. "Bear" that's actually a marsupial
21. Casabas, e.g.
24. A vein in the neck
25. Exhibiting foliage
26. Neighbor of the radius
27. Larynx, colloquially (2 wds.)

DOWN

1. Male whale
2. Back of the head or skull
3. Double's antithesis
4. Konrad who pioneered ethology
6. Antelope with spirally twisted horns
7. Songbird classified as *Dolichonyx oryzivorus*
8. Australian parakeet, affectionately
13. Rainforest mammal with a prehensile tail
15. Resisting chemical change
17. Greek script deciphered by Michael Ventris (2 wds.)
18. Subject of a sonogram
20. Roughly 1 percent of the earth's atmosphere
22. State flower of New Hampshire
23. Wildcat with tufted ears

Answer key on page 5

> We know this is a brain disease. Any idea that this is just willpower and you ought to be able to get over it is completely contrary to what we know on the basis of [the] strongest medical evidence.

—National Institutes of Health Director **Francis Collins**, speaking with the *USA Today* editorial board about the agency's plan to research treatments for opioid addiction (October 3)

> You can think of gender as a variable and if you leave it out, you potentially miss something important in scientific research with human outcomes.

—Stanford University historian **Londa Schiebinger**, who with collaborators recently published a study in *Nature Human Behavior* that proposed ways in which institutions can encourage diversity in terms of both gender and new research directions (October 4)

"Our research has proved that the chicken came not just before the egg, but before anything else in the known universe."

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Notebook

NOVEMBER 2018

MAKING OLD NEW AGAIN: Mount Sinai Hospital researchers Samir Parekh and Deepak Perumal use DNA and RNA sequencing to help find new combinations of existing treatments for cancer patients.

MOUNT SINAI HEALTH SYSTEM

Omics-ing Cancer

At first, Stuart Harshbarger thought he'd injured his back lifting furniture and boxes. When the pain started, in 2008, "we'd just moved from Detroit to New York," he explains. But the pain was excruciating, so the then 45-year-old international management consultant saw a doctor, who tested him for multiple myeloma, a blood cancer that often causes back pain. He got the results by phone while on a business trip in Germany, and was "scared to death," he remembers.

In the decade since, Harshbarger's odyssey has been typical of that of many multiple myeloma patients—though he's made it past the median survival time for the disease, six years. He's been through a series of standard treatments, most of which worked for some time until his cancer developed resistance, prompting his doctors to move him to another therapy. He was able to keep working for most of his time with the disease, but had to go out on disability beginning in mid-2016.

By 2017, "I was just completely out of options," he recalls. At 55 years old, with a wife, one kid in high school and another in college, he was determined to hang on for as long as possible. "Every month that I can stay alive, I can improve and enhance the lives of my [family], who need my help right now," he says. "So we're just struggling for every month we can get, to keep the party going."

That year, Harshbarger entered an immunotherapy trial of autologous CAR T cells engineered to target BCMA, a protein on the surface of multiple myeloma cells. The treatment didn't seem to affect his cancer, and by this time, he was nearly bedridden. What Harshbarger didn't yet know was that his doctors at Mount Sinai Hospital in New York had launched a small clinical trial—not of a new treatment per se, but of a different way of finding treatment options for patients like him.

The six doctors in the hospital's multiple myeloma program see about 3,500 patients each year, says hematologist and oncologist Samir Parekh, many of them referred by other physicians after they stop responding to standard treatments. "The Sinai myeloma program seemed to have a lot of patients that were relapsing, that were either running out of options completely, or going on to clinical trials one after another without any clear biological rationale to guide them," he says.

Parekh, who's trained in genomics, wanted to see if those patients could benefit from a more tailored approach—one that looked beyond standard DNA tests that zoom in on specific loci in cancer cells' genomes. Although such tests have been useful in identifying "actionable mutations"—those that indicate the cells could be vulnerable to a particular drug—in some solid tumors, Parekh says, they've been less effective in blood cancers such as multiple myeloma.

"The problem in myeloma is that patients . . . have drivers that are not entirely clear from just looking at pathology reports, and even DNA sequencing doesn't always give us a clue as to how to manage these patients," Parekh says. "So we had to expand our search beyond the conventional methods." Performing RNA sequencing would give the researchers a peek not just at gene mutations, but at other changes in the cancer cells that might be treatment-relevant, such as copy number variations.

Parekh and colleagues chose 64 of the hospital's patients—including Harshbarger—who had relapsed or were not responding to standard treatments, and sequenced their cancer cells' DNA and messenger RNA. The team was looking for anything that would signal that these patients might respond to drugs that are approved for other cancers but not usually used against multiple myeloma.

The work was painfully slow: sequencing and processing all that data took between four and six weeks for each patient. Parekh and his colleagues identified suggested drugs for all but one of the patients they'd sequenced, but some of their subjects had already died by that time. Others had enrolled in drug trials, and in a few cases, the doctors couldn't get a supply of the recommended drugs. Harshbarger was one of 26 patients who got the recommended personalized treatment. His consisted of dexamethasone, an anti-inflammatory corticosteroid; carfizomib and trametinib, both myeloma treatments; venetoclax, approved for chronic lymphocytic leukemia; and ibrance, a breast cancer drug. "Nothing was working, and all of a sudden, out of a clear blue sky drops this five-drug cocktail," he says.

This is one of the first studies to demonstrate that there's acutally a clinical benefit in doing this.

—Scott Newman
St. Jude Children's Research Hospital

Harshbarger soon felt more energetic, and was able to complete a book he was writing. He experienced a skin reaction, however, and later discontinued the treatment to enter another immunotherapy trial. Harshbarger wasn't alone: 16 of the 21 evaluable patients in Parekh's study responded to the recommended drugs, although only 1 experienced complete remission, and 5 had side effects such as fatigue or diarrhea. The outcomes of the other five patients weren't included in the analysis because they either did not stay on the recommended treatment for long enough, or did not complete the scans and tests needed for evaluation. (*JCO Precis Oncol*, doi:10.1200/PO.18.00019, 2018)

Research on multiple myeloma has "lagged a little behind other cancers, such as solid tumors, in conducting these studies, trying to implement a personalized approach, and incorporating the -omics data in determining treatment," says Hans Lee, a medical oncologist at MD Anderson Cancer Center in Texas who was not involved in the study. "I think this is a great launching pad to exploring further approaches to incorporate such data."

The idea of basing cancer treatment decisions on DNA mutations is not new, although it can be difficult to sift out actionable findings from DNA sequencing data, says computational biologist Scott Newman of St. Jude Children's Research Hospital in Tennessee who was not involved in the study. But adding in transcriptome information is a step forward, he tells *The Scientist*. "To my knowledge, this is one of the first studies to demonstrate that there's actually a clinical benefit in doing this."

Parekh says the number of patients who responded to the recommended treatments was "encouraging," and the team is planning a larger trial of the approach. He'd also like to expand it to other cancers of the blood. One lesson learned from this initial, proof-of-concept study is that the analysis will need to be sped up, he notes, and the hospital is adding equipment and personnel to do just that.

For Harshbarger, who now lives in Greenwich, Connecticut, the personalized treatment has somewhat alleviated his own concern about time. When he spoke with *The Scientist* in August, he had just gone back on the combination therapy devised at Sinai after the second immunotherapy trial had failed to benefit him. Thanks to this cocktail, he was no longer living month to month—but he says he expects his cancer will eventually develop resistance to those drugs, too, leaving him out of options again: "I'm hoping to get a year."

—Shawna Williams

Flash Memory

After publishing a 2014 study showing that noninvasive magnetic stimulation of the brain boosted people's ability to remember an association between two items, Northwestern University neuroscientist Joel Voss began fielding a lot of questions from patients and their families. "We're of course guarded in the publication talking about what we found—small but reliable increases in memory ability," he says (*Science*, 345:1054–57). But some of the news coverage of that

paper alluded to the procedure's potential to treat Alzheimer's disease and other memory-related disorders.

"I got calls—at least two a day for quite a long period of time—and emails: 'My loved one is suffering from X, Y, or Z; thank God now you can cure it. How do we get to your lab?'" Voss says. He would have to explain to them that this was a scientific study, not an approved treatment. "There are a million steps between here and there, and maybe it would never work—we don't really know."

But Voss's team continues to connect those dots, in hopes that one day the technique—the use of magnetic fields to influence activity in neurons close to the brain's surface—could help patients with any number of brain disorders, and perhaps cognitively healthy people as well.

In August, the researchers reported that transcranial magnetic stimulation (TMS) could moderately improve episodic memory—the ability to remember people, events, and other things you've encountered in your life (as opposed to, say, how to do something)—when targeted at the correct part of the brain. Voss and his colleagues were interested in activating the hippocampus, a structure near the brain's center that serves as a hub of memory production and storage. Because the hippocampus itself is inaccessible by TMS—the magnetic field falls off precipitously with depth, explains Voss—the researchers instead targeted areas of the brain where activity correlated with activity in the hippocampus, to try to activate the networks that link more-superficial regions with the deep-brain structure.

The researchers used the technique to target the posterior-medial network in 16 study participants following a memory pretest. Every day for five days in a row, subjects would come to the lab to sit for 20 minutes and allow a researcher to hold a figure-eight-shaped wand to their heads. When participants received the test treatment rather than a sham procedure, the wand emitted a magnetic field that "goes on and off very quickly," Voss says. This field "easily goes into the brain . . . [and] induces electrical activity in the axons of the cortical neurons."

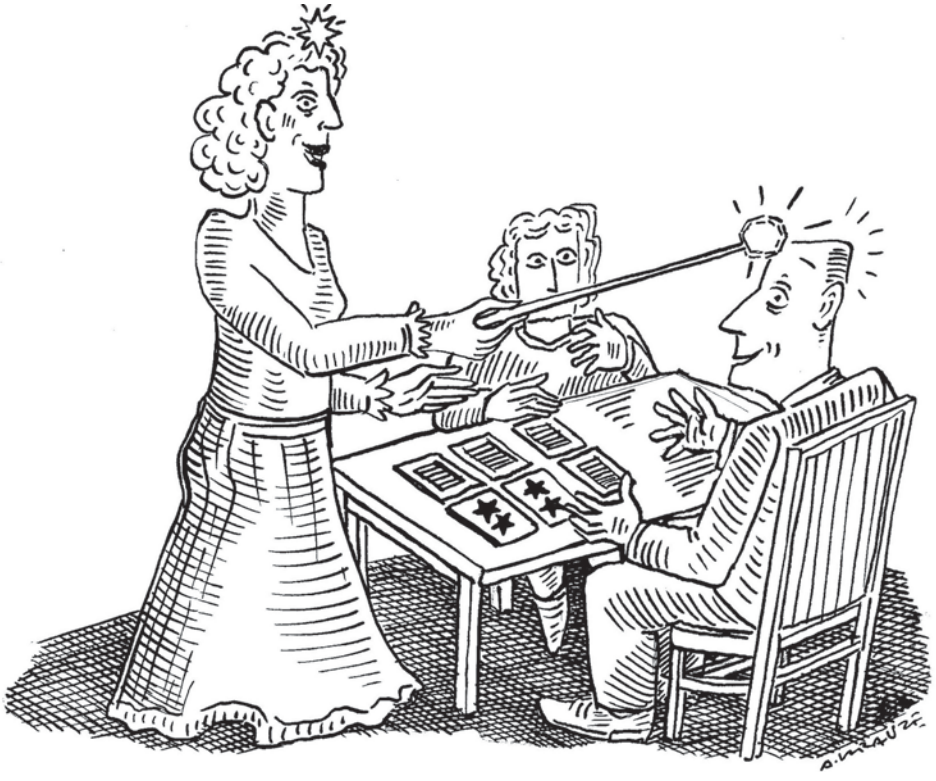
On the sixth day, subjects returned to the lab to have their memory retested. While lying in an fMRI scanner, each person viewed images of, for example, an object or an animal—some of which were displayed within a six-panel grid, and others that were paired with a second image, of an environment. After a short break, participants looked at a series of test images and, for each one, had to report if they recognized it from the first set, and if so, where it had been displayed on the screen or which environmental scene it was paired with.

> **We simply can change the function of this memory network . . . from outside of the head.**
>
> —Joel Voss, Northwestern University

This remembering of location or pairing information exercises an aspect of memory known as recollection. And it is this aspect that was improved by the magnetic stimulation—a result that fits with previous research showing that the targeted cortical-hippocampal network is more involved in recollection than in recognition, or simply knowing whether the object has been previously viewed. What's more, Voss and his colleagues reported that better recollection correlated with activity increases in that network during memory formation, validating the experimental approach (*Sci Adv*, 4:eaar2768, 2018).

"I now have a pretty high level of confidence that we're actually doing something specific to this targeted hippocampal network . . . and what we're doing to it is at some level changing the memory-formation information process," Voss says. "That to me is the most amazing part—just that we simply can change the function of this memory network . . . from outside of the head."

Voss's group isn't the only one trying to boost memory in this noninvasive way. At the University of California, Berkeley,



ANDRZEJ KRAUZE

neuroscientist Mark D'Esposito and his colleagues are using TMS with a different, much shorter protocol—lasting only about 40 seconds. They recently discovered that targeting hippocampal networks using this approach could improve the encoding of new memories (*J Cogn Neurosci*, 30:1452–72, 2018). "It's always good when that happens—slightly different methods but coming to the same conclusions," says Arielle Tambini, a postdoc in D'Esposito's lab and lead author on the study.

More common than magnetic stimulation, though, is the use of electrical pulses in a technique known as transcranial alternating current stimulation (tACS), which a growing body of literature suggests can also boost aspects of memory. "The number of studies that show a positive effect is becoming substantial," says Nick Ketz, a memory researcher at HRL Laboratories in Malibu, California, who recently coauthored a study on the use of tACS to improve memory consolidation during sleep (*J Neurosci*, 38:7314–26, 2018). "It's enough that people are taking notice of it."

But some researchers question the effectiveness of tACS. "It's still not widely accepted, because the mechanism for influence is still a little bit unknown or unreliable," says Ketz. "We haven't determined why it works in some cases and not in others." Moreover, he adds, noninvasive techniques are "still pretty coarse."

During tACS, the scalp and the skull diffuse the voltage, so "it's hard to know where the current is going to flow," Ketz says. Magnetic stimulation isn't influenced by the scalp, and as a result, researchers using methods such as TMS can aim at a specific swatch of cortex more precisely. "We can be much more specific in terms of targeting this brain region versus another brain region that's just a couple of centimeters away," says Tambini.

But all noninvasive approaches face additional shortcomings, says Jon Willie, a neuroscientist and neurosurgeon at Emory University School of Medicine. "Effects may be weak," he notes in an email to *The Scientist*, and "it can be hard to distinguish the effects of arousal, attention, etc., from a specific effect on memory."

When it comes to noninvasively stimulating the brain to boost memory, "really there are more questions than answers yet," agrees Voss, so it's too soon to make claims about the use of these techniques for treating Alzheimer's disease or other brain disorders. For example, he says, "we don't know what the stimulation is doing. . . . What's actually going on neurally is quite a mystery still."

—Jef Akst

Rewired

About three years ago, a six-year-old boy in Pittsburgh underwent surgery to remove a large part of the right side of his brain. Identified publicly as "U.D." by doctors, the boy suffered from epilepsy, and drugs were not helping to control his seizures. His doctors and his parents decided that taking out U.D.'s right occipital and posterior temporal lobes would be the best way to improve his quality of life. But the medical team was not certain how the surgery would affect the boy's ability to recognize visual images

and printed words, which are normally processed by regions within these parts of the brain.

This uncertainty stemmed from neuroscientists not having a clear understanding of how the brain's visual system reorganizes itself after trauma caused by disease, injury, or surgery. "There is a general and ubiquitous question that people who are interested in brain function need to grapple with," says Marlene Behrmann, a psychologist at Carnegie Mellon University in Pittsburgh. "It has to do with the extent to which brain function and even brain structure is concretized or potentially more malleable." U.D.'s surgery and recovery marked an opportunity for Behrmann and her colleagues to address "one small nugget in this much, much larger question," she says.

U.D. is one patient out of many whom Behrmann and her colleagues are now studying to assess the brain's visual system's plasticity—its ability to change—after undergoing a similar surgery. Unlike memory or language processing, which have been explored by many studies of brain recovery following surgery, "there's been really very little work that's looked at reorganization or compensation in the visual system of the brain," she says.

In particular, Behrmann's team is interested in these patients' ability to recognize written words or faces because they are among the most complex stimuli for the visual system to process. To ease the burden on the visual system, a normal brain typically splits responsibility for processing words and faces across the occipital and posterior temporal lobes, with the left-hemisphere sides of those regions recognizing words, and the right-hemisphere sides recognizing faces. "It's not exactly cut-and-dried like that, but one or the other hemisphere bears the burden, to some degree, in each task," Behrmann says. Given this division of labor, she and her colleagues wanted to know what would happen to U.D.'s ability to process images on removal, or resection, of a large portion of the right side of his brain—and more importantly, how his brain might compensate for that loss.

In a paper published in July, the team describes the neurological and cognitive development of the boy during the four years following his lobectomy (*Cell Rep*, 24:1113–22.e6). "We decided to publish that single case ahead of the comprehensive group data because it is the first study that has monitored the change over time in an individual following a resection," Behrmann says. Usually, studies that assess patients' ability to recover cognitive abilities are started many years after surgery rather than just one year afterwards, as this study was.

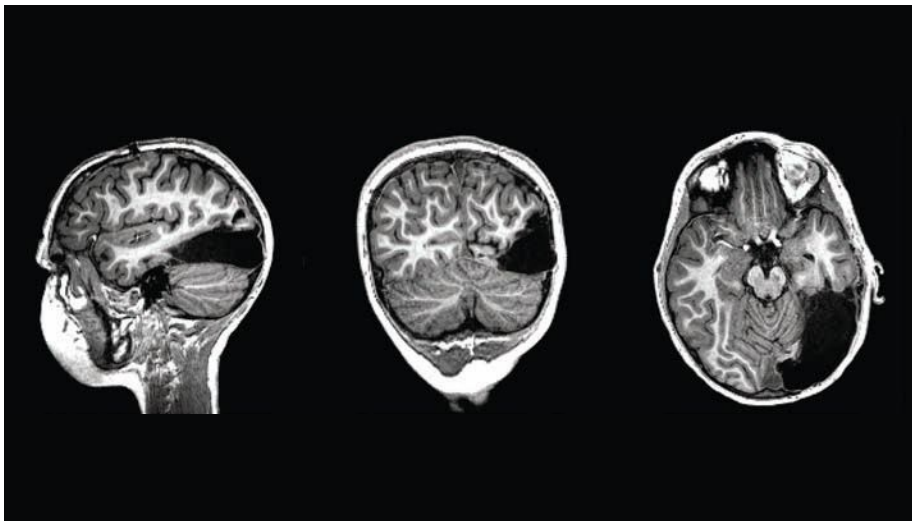
When the researchers examined U.D. 13 months after the operation, they found that the seven-year-old exhibited cognitive skills that were on a par with other kids his age. "We were really surprised that this young child learned to read very well and showed absolutely normal face recognition," says Behrmann. Consequently, "we wanted to know: How did the brain organize itself so that both tasks could be taken on in only one hemisphere?"

Sifting through neuroimaging data collected on several occasions over the three-year period following that first examination, when Berhmann and her colleagues would ask U.D. to identify words or faces, the researchers detected activity in a tiny region of the left hemisphere of his brain during face recognition tasks. This unidentified region sat right next to a different, known region, the visual word form area, that showed activation during word recognition tasks. Although word recognition is normally associated with the visual word form area, face recognition usually is not processed in this part of the brain. "It was as if these two little brain regions were jockeying for position, pushing each other apart," Behrmann says. They were abutting, and only partially overlapping, but allowed for word and face recognition in the single left hemisphere, the researchers concluded.

U.D. hadn't regained all visual functions of the right hemisphere, however. He still was unable to see his left visual field as a result of the surgery, suggesting his brain did not have the plasticity to remap the region in the right hemisphere that processes visual stimuli from the opposite-side visual field. Instead,

Behrmann says, he had to move his eyes or head to bring an object into his right visual field, where it would be processed by the left hemisphere.

"The study is very carefully done and took advantage of a very unique opportunity," writes Isabel Gauthier, a cognitive neuroscientist at Vanderbilt University who studies object perception and was not involved in the work, in an email to *The Scientist*. "The authors certainly got a lot of information out of this one patient, and studies that follow patients over time like this are pretty rare." However, she notes, the data indicate that although U.D. had regained normal face recognition abilities a year after surgery, brain activity in the left hemisphere associated with recognizing faces didn't appear until about a year and seven months after surgery. Based on this observation, "it's unclear what part of his brain he was using for face recognition *before* the resection," Gauthier says. That resection had no effect on his ability to recognize faces, she adds, might mean that face recognition was in fact being processed, both before and after surgery, in an area outside of the large part that was removed.



LIU ET AL., *CELL REPORTS*, 2018

MISSING PIECE: An MRI scan of U.D.'s brain after surgery shows the removal of the right occipital and posterior temporal lobes.

If U.D.'s brain had rewired itself even prior to the surgery, Gauthier notes that it may not have been the procedure but the epilepsy itself that drove this neuronal plasticity—a form of reorganization that

Behrmann and colleagues have explored before. "This is consistent with the idea that when something abnormal—the epilepsy here, not so much the surgery—happens early enough, the brain is better able to reorganize," Gauthier says, noting such plasticity is much more difficult for adult brains.

Behrmann says she and her colleagues did not have presurgical scans of U.D.'s brain to compare with postsurgical ones. However, in subsequent studies of other patients in which they tracked organization and activity both before and after surgery, they found significant differences in the pre- and postsurgical scans, "so we know that the surgery has played a role in bringing about change over and above any that might have come about presurgically because of the epilepsy itself," she says.

"It is really important to understand how the brain is organized around epileptic tissue and how the brain reorganizes itself after surgery," says Taylor Abel, a pediatric neurosurgeon at Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center. Abel, who was not involved in the study or treatment of U.D., specializes in operating on epileptic patients, and is planning to start working with Behrmann soon. The results of the current study are important, he adds, because if paired with future findings from patients similar to U.D., they could help clinicians counsel parents on how their children will respond to surgery, not only for epilepsy, but other types of neurological disorders, too. —Ashley Yeager

Talking Back

In 1995, child psychologists Betty Hart and Todd Risley reported that by age three, children in higher-socioeconomic-status households had heard 30 million more words than their counterparts in lower-socioeconomic-status homes. This so-called word gap has often been invoked to explain why children in the former category tend to display better language skills and perform better in school compared to those from underprivileged homes—with effects that reverberate throughout their lives.

"Language is implicated in school achievement, social emotional growth, in health outcomes [and] in job outcomes when you're a grown-up," says Roberta Golinkoff, who leads the Child's Play, Learning, and Development laboratory at the University of Delaware. "Language predicts all these."

But researchers have struggled to gain a mechanistic understanding of this phenomenon. "What people are discovering is that socioeconomic status is really just a proxy variable," says Rachel Romeo, a postdoc in developmental cognitive neuroscience at MIT and Boston Children's Hospital. Although factors such as household income and parental education are associated with a child's learning abilities, researchers suspect there are features of the home learning environment, such as the amount of time adults spend talking to their children, that have a more direct influence. But few studies have been able to measure these environmental effects on learning ability, as they are difficult to disentangle from a family's socioeconomic status, notes Romeo.

> **Socioeconomic status is really just a proxy variable.**
>
> —Rachel Romeo
> MIT & Boston Children's Hospital

To dig deeper, she and her colleagues recently set out to determine the neural underpinnings of language ability differences across the socioeconomic spectrum. First, Romeo and her team measured the language exposure of 40 children between the ages of 4 and 6 from various backgrounds. Each child carried around an audio recorder for a single weekend in 2015 or 2016 within the pocket of a specially designed T-shirt, a setup that helped capture a child's language environment from his or her perspective. Then, the researchers used analytical software to count the number of conversational turns—one turn being measured as a pair of adult and child responses separated by five seconds or less—occurring over every hour for the 48-hour period.

The team conducted the second part of their study back in the laboratory, where parents and children who had taken part in the recordings underwent MRI scans. In their analyses, Romeo and her colleagues specifically focused on white matter tracts, or the "information highways" connecting different regions of the participants' brains, Romeo says. "We were looking at the strength of these connections in various parts of the brain."

The researchers found that tracts running between regions of the brain known to be important for language development in the left hemisphere had a more coherent structure in children who shared greater turn-taking with their parents. On average, those children had greater white matter connectivity between Broca's area and Wernicke's area, two regions associated with speech production and comprehension (*J Neurosci*, 38:7870–77, 2018).

The results indicate that two-way adult-child conversation—independent of the child's socioeconomic status and the number of words a child hears—can strengthen neural pathways involved in language. "Our research suggests that it's not really the volume of language children hear, but really about the quality of the conversation—this back-and-forth dialogue," says Romeo.

"This study has added an interesting additional variable that helps our explanatory power of why [lower socioeconomic status] might be associated with poor language outcomes," says Rachel Barr, the director of Georgetown University's Early Learning Project, who was not involved in this study. She adds that parents in these families may have fewer opportunities to share dialogue with their children—and that interventions focused on conversational turn-taking could help. "It's not just, 'Add words, and the child's language

BEING HEARD: The degree of turn-taking in conversation with adults, not the volume of words, drives the development of children's language skills, a new study suggests.

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will develop,'" she says. "It's rather that language is a communication process, and the child needs to learn when it's their turn."

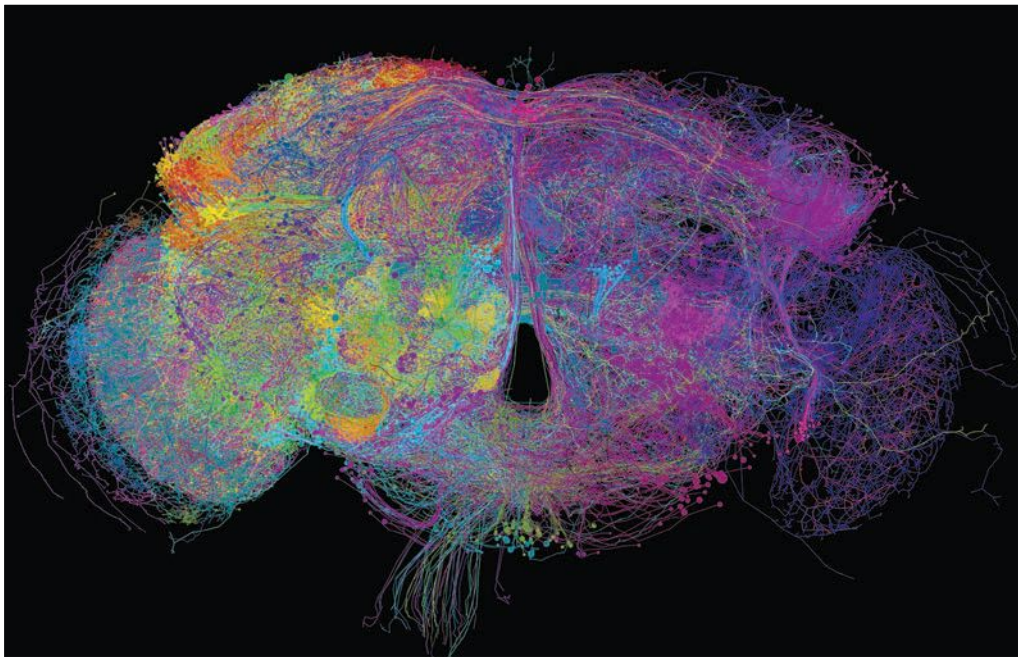
Romeo says that "there's been a lot of dissemination of research in the last couple of decades saying that children need to hear X amount of words a day. [It] creates sort of this phenomenon where parents are monologuing to their children and just saying words just to get them in—almost like there's a quota." Golinkoff notes that it's also important to realize that ambient sounds from the TV or radio, like conversations that do not involve the child in turn-taking, may have little impact on the learning abilities of children.

Romeo's advice: "Instead of talking to your children, really try and talk *with* them; let them respond," she says. "Have an exchange of information rather than just a one-sided discussion."

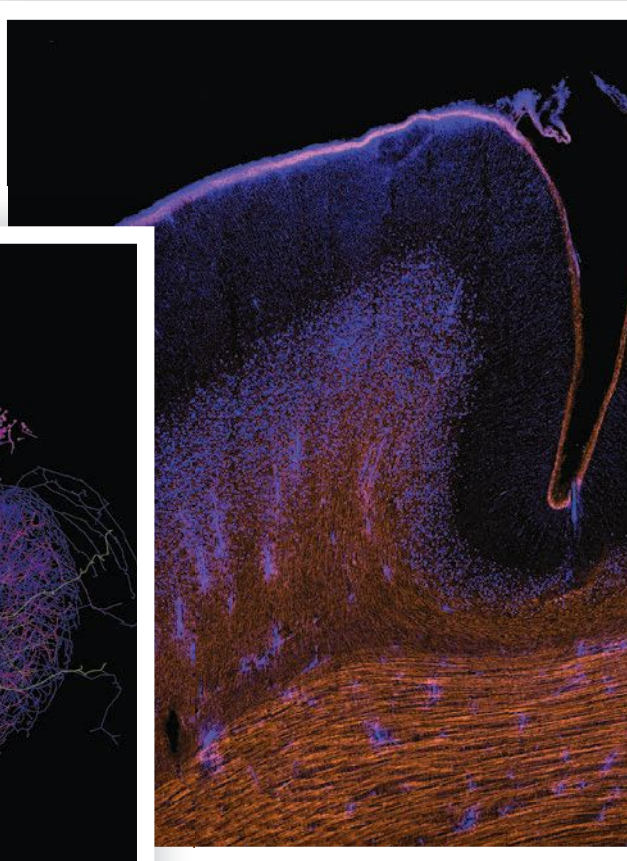
—Sukanya Charuchandra

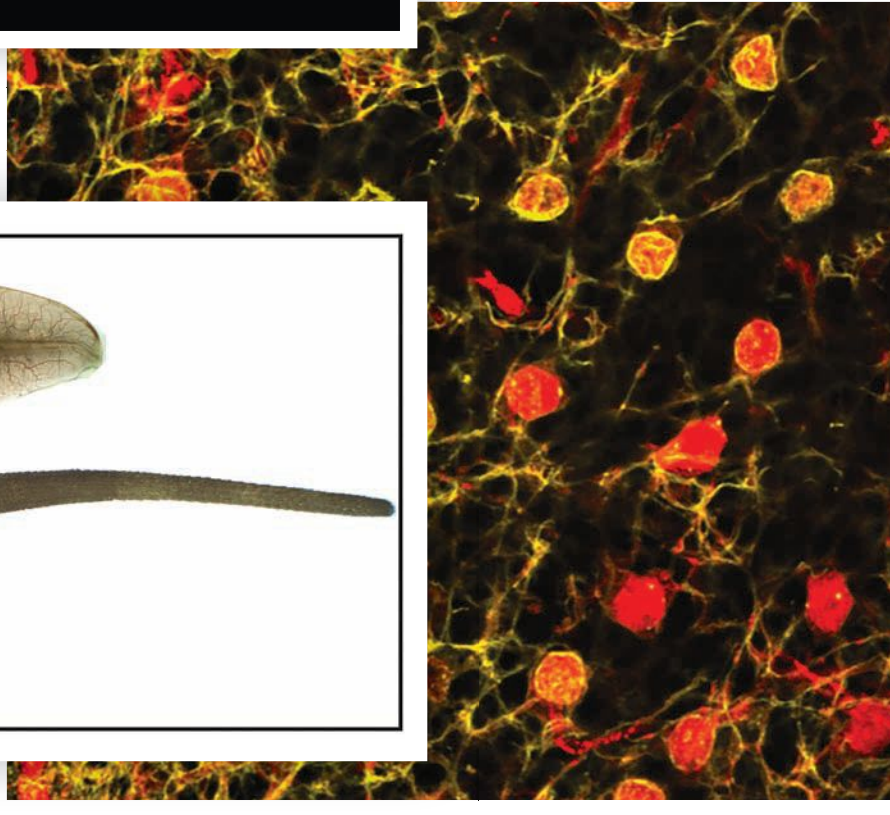
Caught on Camera

Selected Images of the Day from the-scientist.com

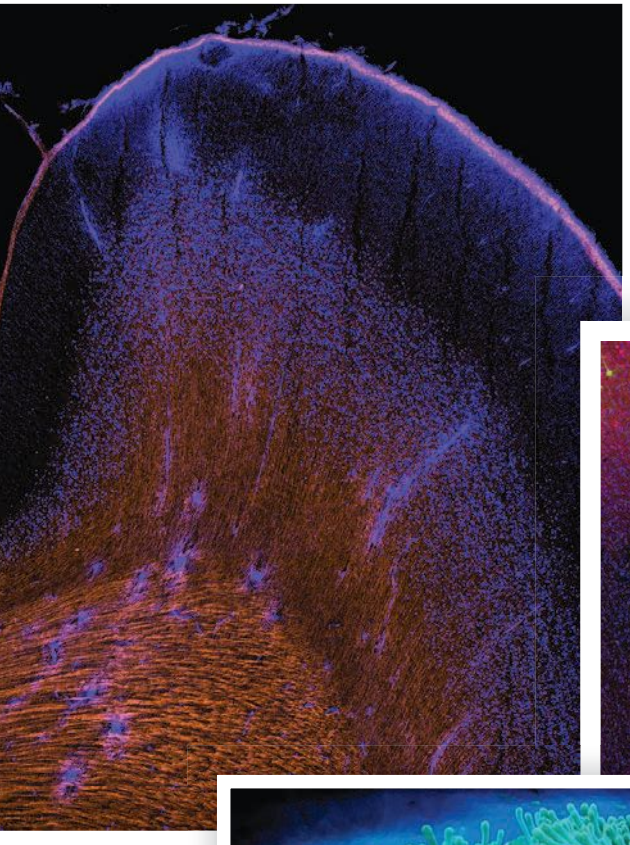


SNAPSHOT
A map of the entire fruit-fly brain details the positions and connections of roughly 100,000 neurons.
Posted: *July 20, 2018*





REVIVAL
The varying regenerative properties of amphibian, reptile, and mammal tails result from differences in neural stem cells found in the animals' spinal cords, according to a recent study.
Posted: *August 17, 2018*

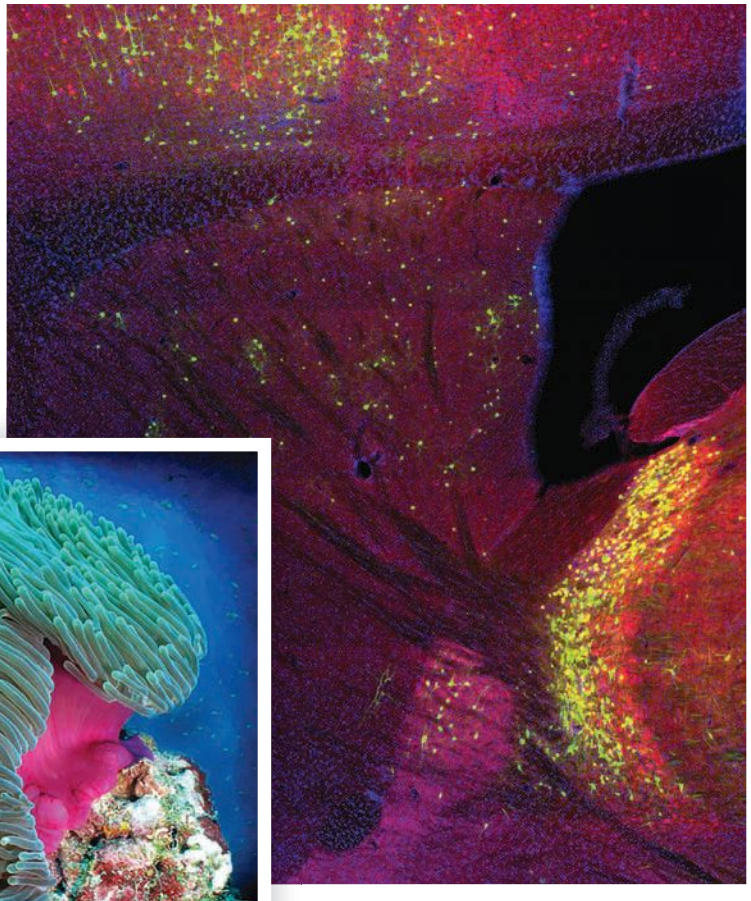


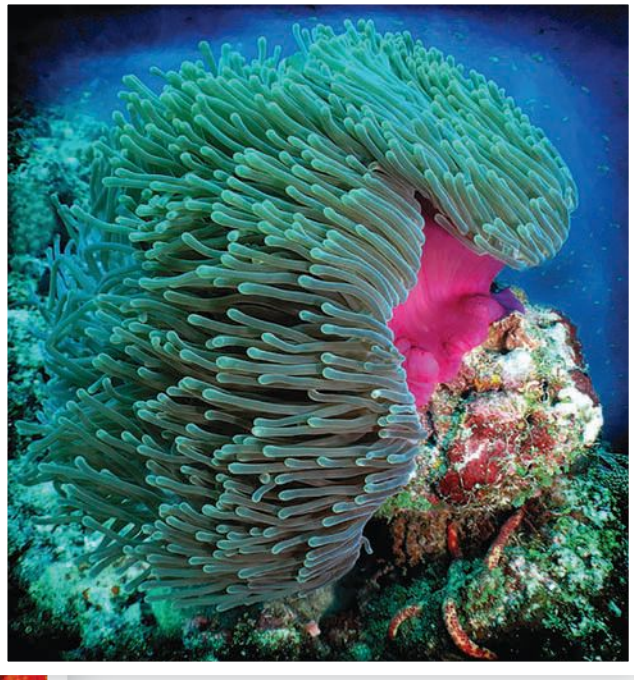
« HIDE AND SEEK

Scientists reported this year that the subplate, a predominant layer (bright blue region above the orange cells) of the developing brain, does not disappear in adults, as previously thought.
Posted: *June 26, 2018*

» THE FIVE PERCENT

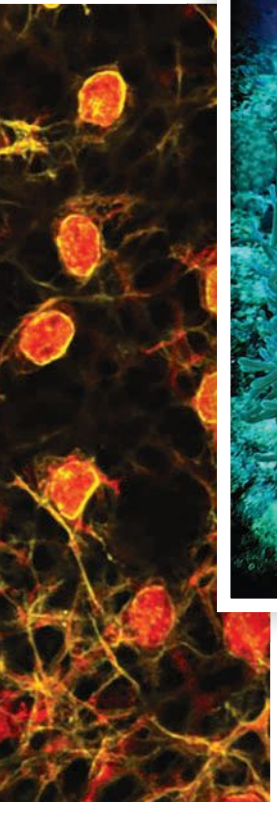
A recently published map of neural networks in the striatum (green dots in center) of the mouse brain reveals previously underappreciated connections.
Posted: *May 7, 2018*





« OCEAN WONDER

Synthetic molecules similar to those produced by sea anemones, such as this *Heteractis magnifica*, are neuroprotective in a mouse cell model of Alzheimer's disease.
Posted: *September 4, 2018*



« THROW THE SWITCH

A computer model of the mouse retina can predict the consequences of altering the function of neurons, such as these horizontal cells.
Posted: *June 27, 2018*

Snapshot: Z. Zheng et al., *Cell*, doi:10.1016/j.cell.2018.06.019, 2018. Visualization by Philipp Schlegel (*Drosophila* connectomics group, Cambridge); **Revival:** A.X. Sun et al., *PNAS*, doi:10.1073/pnas.1803780115, 2018. Courtesy of Thomas P. Lozito; **Hide and Seek:** M.Z. Ozair et al., *Cell Stem Cell*, doi:10.1016/j.stem.2018.05.024, 2018. Courtesy of the Laboratory of Stem Cell Biology and Molecular Embryology at the Rockefeller University; **Throw the Switch:** A. Drinnernberg et al., *Neuron*, doi:10.1016/j.neuron.2018.06.001, 2018.; **The Five Percent**: J.R. Klug et al., *eLife*, 10.7554/eLife.35657, 2018. Courtesy of the Salk Institute; **Ocean Wonder:** A.N. Kvetkina et al., *Russ J Bioorg Chem+*, doi:10.1134/S106816201804012X, 2018. Courtesy of Neville Wootton

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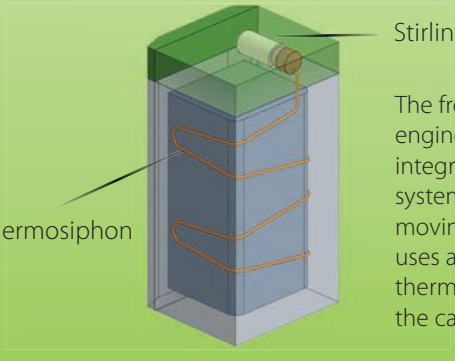

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Retina Recordings Reinvented

Ultraflexible mesh electrodes monitor intact, functioning eyes of awake animals.

BY RUTH WILLIAMS

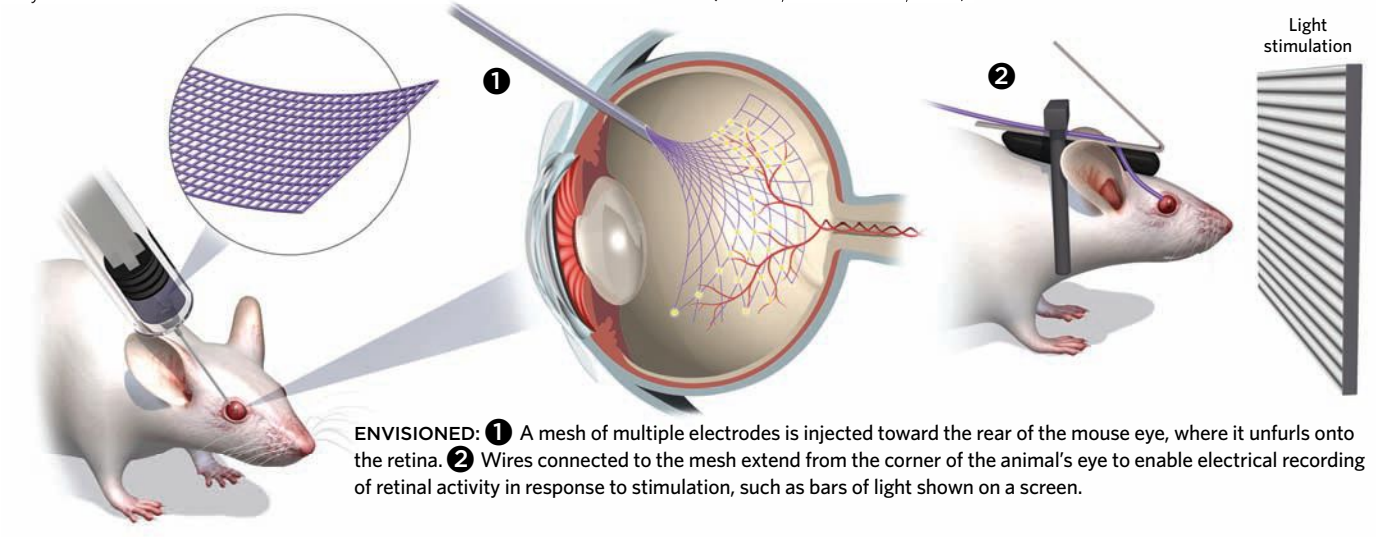
The eye presents a paradox to experimental neuroscientists. On one hand, it's accessible, its function is well understood, and its inputs can be precisely controlled, says neurobiologist William Newsome of Stanford University. "On the other hand, it is very difficult to record its electrical signals while visual behavior is actually taking place." That's because the hardware for electrical recordings—rigid electrodes—aren't compatible with small, spherical, constantly moving rodent eyes.

To record retinal cell activity, researchers tend to remove the eye from the animal, dissect the retina, and lay it flat on an array of microelectrodes. While such preparations can continue to respond to light for a matter of hours, new mesh electrodes, developed by nanotechnologist Charles Lieber of Harvard University and colleagues, can remain inside a living animal's eye, recording the same cells for several weeks.

Measuring 1.5 mm by 0.8 mm and containing 16 individual electrodes, the polymer and metal meshes are injected, one per mouse eye, toward the rear of the vitreous body, where they unfurl to coat the retina. Tiny wires connected to the meshes extend out of the corner of the animals' eyes for attachment to an external recording device. The animals are restrained, their heads immobilized, for sessions of light stimulation and recording, but they are free to move and behave normally between sessions. Remarkably, the meshes have little effect on vision, and after a few weeks they detach from the retina.

Long-term, in vivo recording ability opens a range of new research avenues, says Lieber, whose team has used the meshes to measure changes in retinal ganglion cell activity over the course of several day/night cycles.

It's a "fantastic" innovation, says Marla Feller of the University of California, Berkeley, who studies the organization of retinal neural circuits during development but was not involved in the research. "It was exciting to see how successful it was at being able to record from the same cells over multiple days." Not only might the method be useful for following individual cells through retinal maturation, she says, but also for examining which cells die and which survive during eye diseases such as glaucoma. (*Science*, 360:1447–51, 2018) ■



ENVISIONED: ❶ A mesh of multiple electrodes is injected toward the rear of the mouse eye, where it unfurls onto the retina. ❷ Wires connected to the mesh extend from the corner of the animal's eye to enable electrical recording of retinal activity in response to stimulation, such as bars of light shown on a screen.

AT A GLANCE

MULTI-CELL RETINAL RECORDINGS	METHOD	VIABLE RECORDING TIME	NO. OF SIMULTANEOUSLY RECORDING ELECTRODES	INVASIVE?
Ex vivo	The eye is removed, and the retina is dissected and laid flat on an array of microelectrodes.	8 to 12 hours for mouse retinas	Approximately 500	Highly. Animal sacrificed
In vivo	Mesh electrode is injected into the eye of an anesthetized mouse.	Several weeks	16 so far but could theoretically be more	Minimally. Visual function negligibly affected

The Intelligence Puzzle

Imaging, behavioral, and genetic data yield clues to what's behind effective thinking.

BY SHAWNA WILLIAMS

In 1987, political scientist James Flynn of the University of Otago in New Zealand documented a curious phenomenon: broad intelligence gains in multiple human populations over time. Across 14 countries where decades' worth of average IQ scores of large swaths of the population were available, all had upward swings—some of them dramatic. Children in Japan, for example, gained an average of 20 points on a test known as the Wechsler Intelligence Scale for Children between 1951 and 1975. In France, the average 18-year-old man performed 25 points better on a reasoning test in 1974 than did his 1949 counterpart.

Flynn initially suspected the trend reflected faulty tests. Yet in the ensuing years, more data and analyses supported the idea that human intelligence was increasing over time. Proposed explanations for the phenomenon, now known as the Flynn effect, include increasing education, better nutrition, greater use of technology, and reduced lead exposure, to name but four. Beginning with people born in the 1970s, the trend has reversed in some Western European countries, deepening the mystery of what's behind the generational fluctuations. But no consensus has emerged on the underlying cause of these trends.

A fundamental challenge in understanding the Flynn effect is defining intelligence. At the dawn of the 20th century, English psychologist Charles Spearman first observed that people's average performance on a variety of seemingly unrelated mental tasks—judging whether one weight is heavier than another, for example, or pushing a button quickly after a light comes on—predicts our average performance on a completely different set of tasks. Spearman proposed that a single measure of general intelligence, *g*, was responsible for that commonality.

Scientists have proposed biological mechanisms for variations among individuals' *g* levels ranging from brain size and density to the synchrony of neural activity to overall connectivity within the cortex. But the precise physiological origin of *g* is far from settled, and a simple explanation for differences in intelligence between individuals continues to elude researchers. A recent study of 1,475 adolescents across Europe reported that intelligence, as measured by a cognitive test, was associated with a panoply of biological features, including known genetic markers, epigenetic modifications of a gene involved in dopamine signaling, gray matter density in the striatum (a major player in motor control and reward response), and the striatum's activation in response to a surprising reward cue.

Understanding human smarts has been made even more challenging by the efforts of some inside and outside the field to introduce pseudoscientific concepts into the mix. The study of intelligence has at times been tainted by eugenics, "scientific" racism, and sexism, for example. As recently as 2014, former *New York Times* science writer Nicholas Wade drew fire for what critics characterized as misinterpreting genetics studies to suggest race could correlate with average differences in intelligence and other traits. The legitimacy of such analyses aside, for today's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intelligence researchers, categorization isn't the end goal.

"The reason I'm interested in fluid intelligence tests"—which home in on problem-solving ability rather than learned knowledge—"is not really because I want to know what makes one person do better than another," says University of Cambridge neuroscientist John Duncan. "It's important for everybody because these functions are there in everybody's mind, and it would be very nice to know how they work."

In search of *g*

G, and the IQ (or intelligence quotient) tests that aim to measure it, have proven remarkably durable since Spearman's time. Multiple studies have backed his finding of a measurable correlation among an individual's performances on disparate cognitive tests. And *g* interests researchers because its effects extend far beyond academic and work performance. In study after study, higher IQ is tied to outcomes such as greater income and educational attainment, as well as to lower risks of chronic disease, disability, and early death.

Early studies of people with brain injuries posited the frontal lobes as vital to problem solving. In the late 1980s, Richard Haier of the University of California, Irvine, and colleagues imaged the brains of people as they solved abstract reasoning puzzles, which revved up specific areas in the frontal, parietal, and occipital lobes of the brain, as well as communication between them. The frontal lobes are associated with planning and attention; the parietal lobes interpret sensory information; and the occipital lobe processes visual information—all abilities useful in puzzle solving. But more activity didn't mean greater cognitive prowess, notes Haier. "The people with the highest test scores actually showed the lowest brain activity, suggesting that it wasn't how hard your brain was working that made you smart, but how efficiently your brain was working."

In 2007, based on this and other neuroimaging studies, Haier and the University of New Mexico's Rex Jung proposed the parieto-frontal integration theory, arguing that the brain areas identified in Haier's and others' studies are central to intelligence. (See illustration on page 31.) But Haier and other researchers have since found that patterns of activation vary, even between people of similar intelligence, when performing the same mental tasks. This suggests, he says, that there are different pathways that the brain can use to reach the same end point.

Another problem with locating the seat of *g* via brain imaging, some argue, is that our instruments are still simply too crude to yield satisfying answers. Haier's PET scans in the 1980s, for instance, tracked radiolabeled glucose through the brain to get a picture of metabolic activity during a 30-minute window in an organ whose cells communicate with one another on the order of milliseconds. And modern fMRI scans, while more temporally precise, merely track blood flow through the brain, not the actual activity of individual neurons. "It's like if you're trying to understand the principles of human speech and all you could listen to is the volume of noise coming out of a whole city," Duncan says.

The people with the highest test scores actually showed the lowest brain activity, suggesting that it wasn't how hard your brain was working that made you smart, but how efficiently your brain was working.

—Richard Haier, University of California, Irvine

Models of intelligence

Beyond simply not having sharp-enough tools, some researchers are beginning to question the premise that the key to intelligence can be seen in the anatomical features of the brain. "The dominant view of the brain in the 20th century was anatomy is destiny," says neurophysiologist Earl Miller of MIT's Picower Institute for Learning and Memory; but it's become clear over the past 10 to 15 years that this view is too simplistic.

Researchers have begun to propose alternative properties of the brain that might undergird intelligence. Miller, for example, has been tracking the behavior of brain waves, which arise when multiple neurons fire in synchrony, for clues about IQ. In one recent study, he and colleagues hooked up EEG electrodes to the heads of monkeys that had been taught to release a bar if they saw the same sequence of objects they'd seen a moment before. The task relied on working memory, the ability to access and store bits of relevant information, and it caused bursts of high-frequency γ and lower-frequency β waves. When the bursts weren't synchronized at the usual points during the task, the animals made errors.

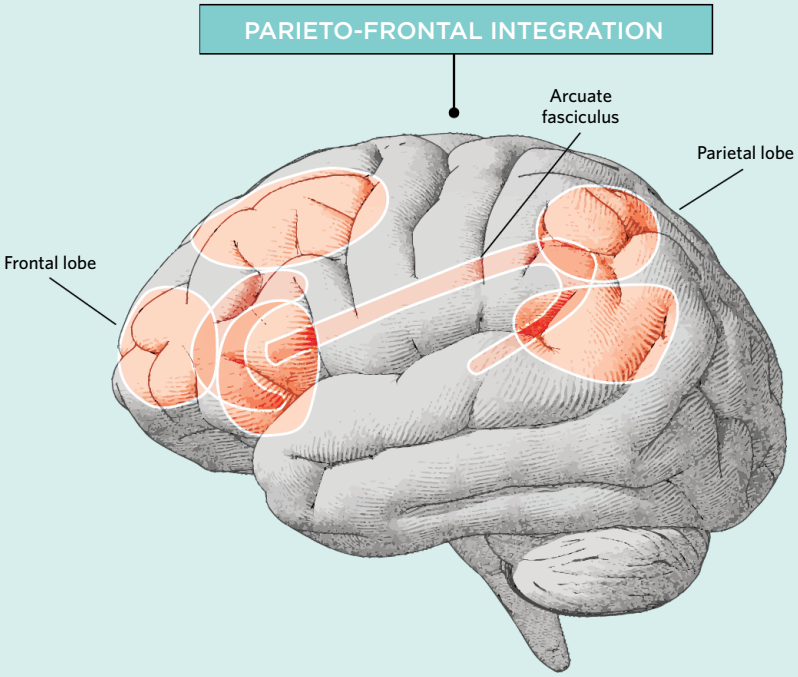
Miller suspects that these waves "direct traffic" in the brain, ensuring that neural signals reach the appropriate neurons when they need to. "Gamma is bottom-up—it carries the contents of what you're thinking about. And beta is top-down—it carries the control signals that determine what you think about," he says. "If your beta isn't strong enough to control the gamma, you get a brain that can't filter out distractions."

The overall pattern of brain communications is another candidate to explain intelligence. Earlier this year, Aron Barbey, a psychology researcher at the University of Illinois at Urbana-Champaign, proposed this idea, which he calls the network neuroscience theory, citing studies that used techniques such as diffusion tensor MRI to trace the connections among brain regions. Barbey is far from the first to suggest that the ability of different parts of the brain to communicate with one another is central to intelligence, but the whole-brain nature of network neuroscience theory contrasts with more established models, such as parieto-frontal integration theory, that focus on specific regions. "General intelligence originates from individual differences in the system-wide topology and dynamics of the human brain," Barbey tells *The Scientist*.

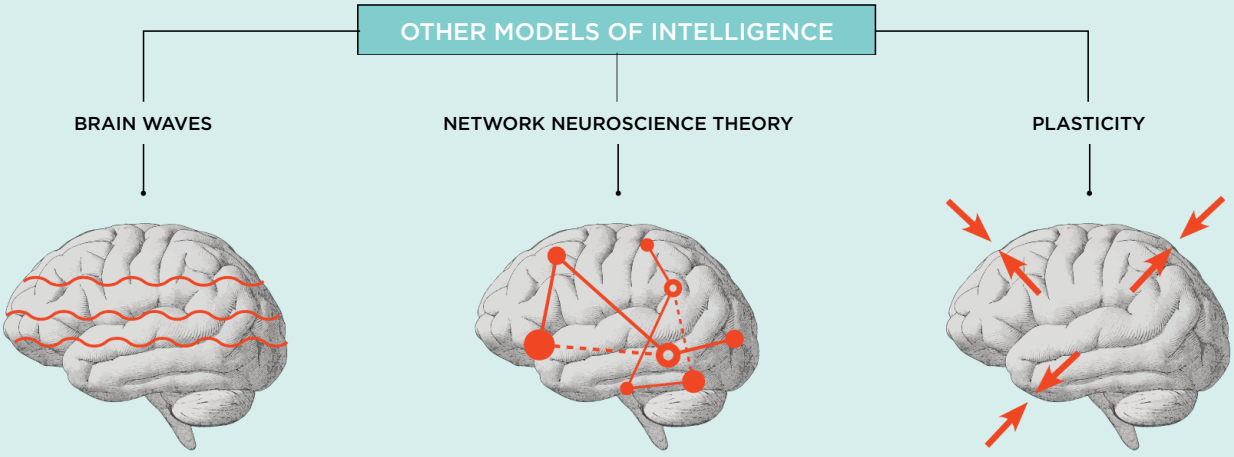
Emiliano Santarnecchi of Harvard University and Simone Rossi of the University

PARSING SMARTNESS

The biological basis for variations in human intelligence is not well understood, but research in neuroscience, psychology, and other fields has begun to yield insights into what may undergird such differences. One well-known hypothesis, backed by evidence from brain scans and studies of people with brain lesions, proposes that intelligence is seated in particular clusters of neurons in the brain, many of them located in the prefrontal and parietal cortices. Known as the fronto-parietal integration, the hypothesis holds that the structure of these areas, their activity, and the connections between them vary among individuals and correlate with performance on cognitive tasks.



Researchers have also proposed a slew of other hypotheses to explain individual variation in human intelligence. The variety of proposed mechanisms underlines the scientific uncertainty about just how intelligence arises. Below are three of these hypotheses, each backed by experimental evidence and computational modeling:



Coordination of β and γ waves, produced by neurons firing in synchrony in the cortex, is needed to complete cognitive tasks.

Intelligence arises from the way the whole brain communicates within itself.

The response of brain activity patterns to changes—such as transcranial stimulation or learning—is key to intelligence.

THE SCIENTIST STAFF

of Siena in Italy also argue that intelligence is a property of the whole brain, but they see overall plasticity as the key to smarts. Plasticity, the brain's ability to reorganize, can be measured via the nature of the brain activity generated in response to transcranial magnetic or electrical stimulation, Santarnecchi says. "There are individuals that generate a response that is only with the other nodes of the same network that we target," he says. And then there are people in whose brains "the signal starts propagating everywhere." His group has found that higher intelligence, as measured by IQ tests, corresponds with a more network-specific response, which Santarnecchi hypothesizes "reflects some sort of … higher efficiency in more-intelligent brains."

> General intelligence originates from individual differences in the system-wide topology and dynamics of the human brain.
>
> —Aron Barbey, University of Illinois at Urbana-Champaign

Despite the hints uncovered about how intelligence comes about, Santarnecchi finds himself frustrated that research has not yielded more-concrete answers about what he considers one of neuroscience's central problems. To address that shortcoming, he's now spearheading a consortium of cognitive neuroscientists, engineers, evolutionary biologists, and researchers from other disciplines to discuss approaches for getting at the biological basis of intelligence. Santarnecchi would like to see manipulations of the brain—through noninvasive stimulation, for example—to get at causal relationships between brain activity and cognitive performance. "We know a lot now about intelligence," he says, "But I think it's time to try to answer the question in a different way."

Putting the *g* in genes

As neuroscientists interrogate the brain for how its structure and activity relate to intelligence, geneticists have approached intelligence from a different angle. Based on what they've found so far, psychology researcher Sophie von Stumm of the London School of Economics estimates that about 25 percent of individual variation in intelligence will turn out to be explained by single nucleotide polymorphisms in the genome.

To find genes at play in intelligence, researchers have scanned the genomes of thousands of people. Earlier this year, for example, economist Daniel Benjamin of the University of Southern California and colleagues crunched data on upwards of 1.1 million subjects of European descent and identified more than 1,200 sites in the genome associated with educational attainment, a common proxy for intelligence. Because subjects in many types of medical studies in which DNA is sequenced are asked about their educational status to help control for socioeconomic factors in later analyses, such data are plentiful. And while the correlation between education and intelligence is imperfect, "intelligence and school achievement are highly correlated, and genetically very highly correlated," says von Stumm, who recently coauthored a review on the genetics of intelligence. Altogether, the genes identified so far accounted for about 11 percent of individual variation in education level in Benjamin's study; household income, by comparison, explained 7 percent.

Such genome-wide association studies (GWAS) have been limited in what they reveal about the biology at work in intelligence and educational attainment, as much remains to be learned about the genes thus far identified. But there have been hints, says Benjamin. For example, the genes with known functions that turned up in his recent study "seem to be involved in pretty much all aspects of brain development and neuron-to-neuron communication, but not glial cells," Benjamin says. Because glial cells affect how quickly neurons transmit signals to one another, this suggests that firing speed is not a factor in differences in educational attainment.

Other genes seem to link intelligence to various brain diseases. For example, in a preprint GWAS published last year, Danielle Posthuma of VU University Amsterdam and colleagues identified associations between cognitive test scores and variants that are negatively correlated with depression, ADHD, and schizophrenia, indicating a possible mechanism for known correlations between intelligence and lower risk for mental disorders. The researchers also found intelligence-associated variants that are positively correlated with autism.

Von Stumm is skeptical that genetic data will yield useful information in the near term about how intelligence results from the brain's structure or function. But GWAS can yield insights into intelligence in less direct ways. Based on their results, Benjamin and colleagues devised a polygenic score that correlates with education level. Although it's not strong enough to be used to predict individuals' abilities, Benjamin says the score should prove useful for researchers, as it enables them to control for genetics in analyses that aim to identify environmental factors that influence intelligence. "Our research will allow for better answers to questions about what kinds of environmental interventions improve student outcomes," he says.

Von Stumm plans to use Benjamin's polygenic score to piece together how genes and environment interact. "We can test directly for the first time," says von Stumm, "if children who grow up in impoverished families … with fewer resources, if their genetic differences are as predictive of their school achievement as children who grow up in wealthier families, who have all the possibilities in the world to grab onto learning opportunities that suit their genetic predispositions."

Thinking about thinking

It's not just the biology of intelligence that remains a black box; researchers are still trying to wrap their minds around the concept itself. Indeed, the idea that *g* represents a singular property of the brain has been challenged. While *g*'s usefulness and predictive power as an index is widely accepted, proponents of alternative mod-

els see it as an average or summation of cognitive abilities, not a cause.

Last year, University of Cambridge neuroscientist Rogier Kievit and colleagues published a study that suggests IQ is an index of the collective strength of more-specialized cognitive skills that reinforce one another. The results were based on vocabulary and visual reasoning test scores for hundreds of UK residents in their late teens and early 20s, and from the same subjects about a year and a half later. With data on the same people at two time points, Kievit says, the researchers could examine whether performance on one cognitive skill, such as vocabulary or reasoning, could predict the rate of improvement in another domain. Using algorithms to predict what changes should have occurred under various models of intelligence, the researchers concluded that the best fit was mutualism, the idea that different cognitive abilities support one another in positive feedback loops.

In 2016, Andrew Conway of Claremont Graduate University in California and Kristóf Kovács, now of Eötvös Loránd University in Hungary, made a different argument for the involvement of multiple cognitive processes in intelligence. In their model, application-specific neural networks—those needed for doing simple math or navigating an environment, for example—and high-level, general-purpose executive processes, such as breaking down a problem into a series of small, manageable blocks, each play a role in helping a person complete cognitive tasks. It's the fact that a variety of tasks tap into the same executive processes that explains why individuals' performance on disparate tasks correlates, and it's the average strength of these higher-order processes, not a singular ability, that's measured by *g*, the researchers argue. Neuroscientists might make more progress in understanding intelligence by looking for the features of the brain that carry out particular executive processes, rather than for the seat of a single *g* factor, Kovács says.

As researchers grapple with the intractable phenomenon of intelligence, a philosophical question arises: Is our species smart enough to understand the basis of our own intelligence? While those in the field generally agree that science has a long way to go to make sense of how we think, most express cautious optimism that the coming decades will yield major insights.

"We see now the development, not only of mapping brain connections in human beings . . . we're also beginning to see synapse mapping," Haier says. "This will take our understanding of the basic biological mechanisms of things like intelligence . . . to a whole new level." ■

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UPPING IQ

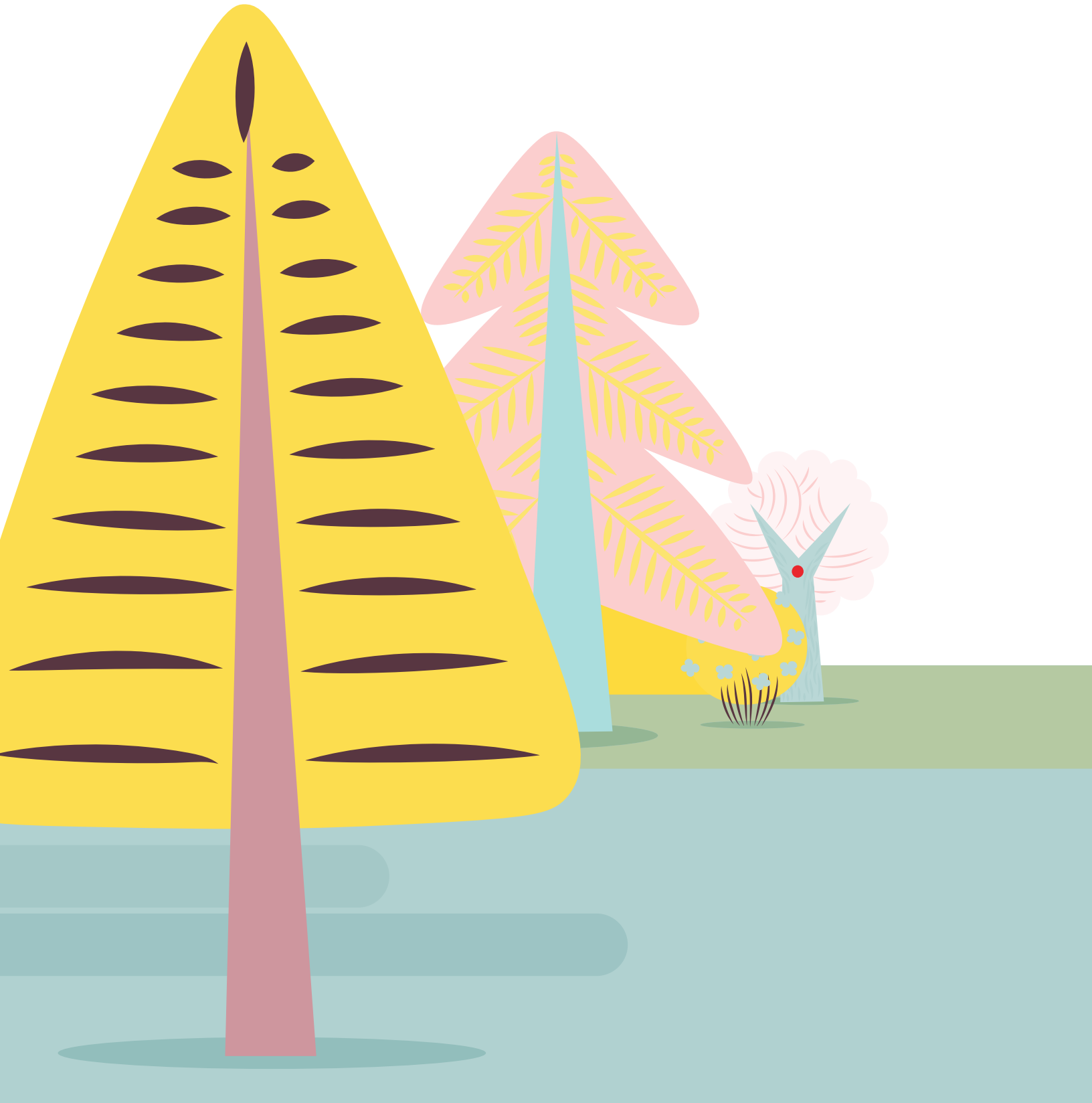
The idea of manipulating intelligence is enticing, and there has been no shortage of efforts to do just that. One tactic that once seemed to hold some promise for increasing intelligence is the use of brain-training games. With practice, players improve their performance on these simple video games, which rely on skills such as quick reaction time or short-term memorization. But reviews of numerous studies found no good evidence that such games bolster overall cognitive abilities, and brain training of this kind is now generally considered a disappointment.

Transcranial brain stimulation, which sends mild electrical or magnetic pulses through the skull, has shown some potential in recent decades for enhancing intelligence. In 2015, for example, neurologist Emiliano Santarnecchi of Harvard Medical School and colleagues found that subjects solved puzzles faster with one type of transcranial alternating current stimulation, while a 2015 meta-analysis found "significant and reliable effects" of another type of electrical stimulation, transcranial direct current stimulation (*Curr Biol*, 23:1449–53).

While magnetic stimulation has yielded similarly enticing results, studies of both electrical and magnetic stimulation have also raised doubts about the effectiveness of these techniques, and even researchers who believe they can improve cognitive performance admit that we're a long way from using them clinically. (See "Flash Memory" on page 17.)

One proven way researchers know to increase intelligence is good old-fashioned education. In a meta-analysis published earlier this year, a team led by then University of Edinburgh neuropsychologist Stuart Ritchie (now at King's College London) sifted out confounding factors from data reported in multiple studies and found that schooling—regardless of age or level of education—raises IQ by an average of one to five points per year (*Psychol Sci*, 29:1358–69). Researchers, including University of British Columbia developmental cognitive neuroscientist Adele Diamond, are working to understand what elements of education are most beneficial to brains.

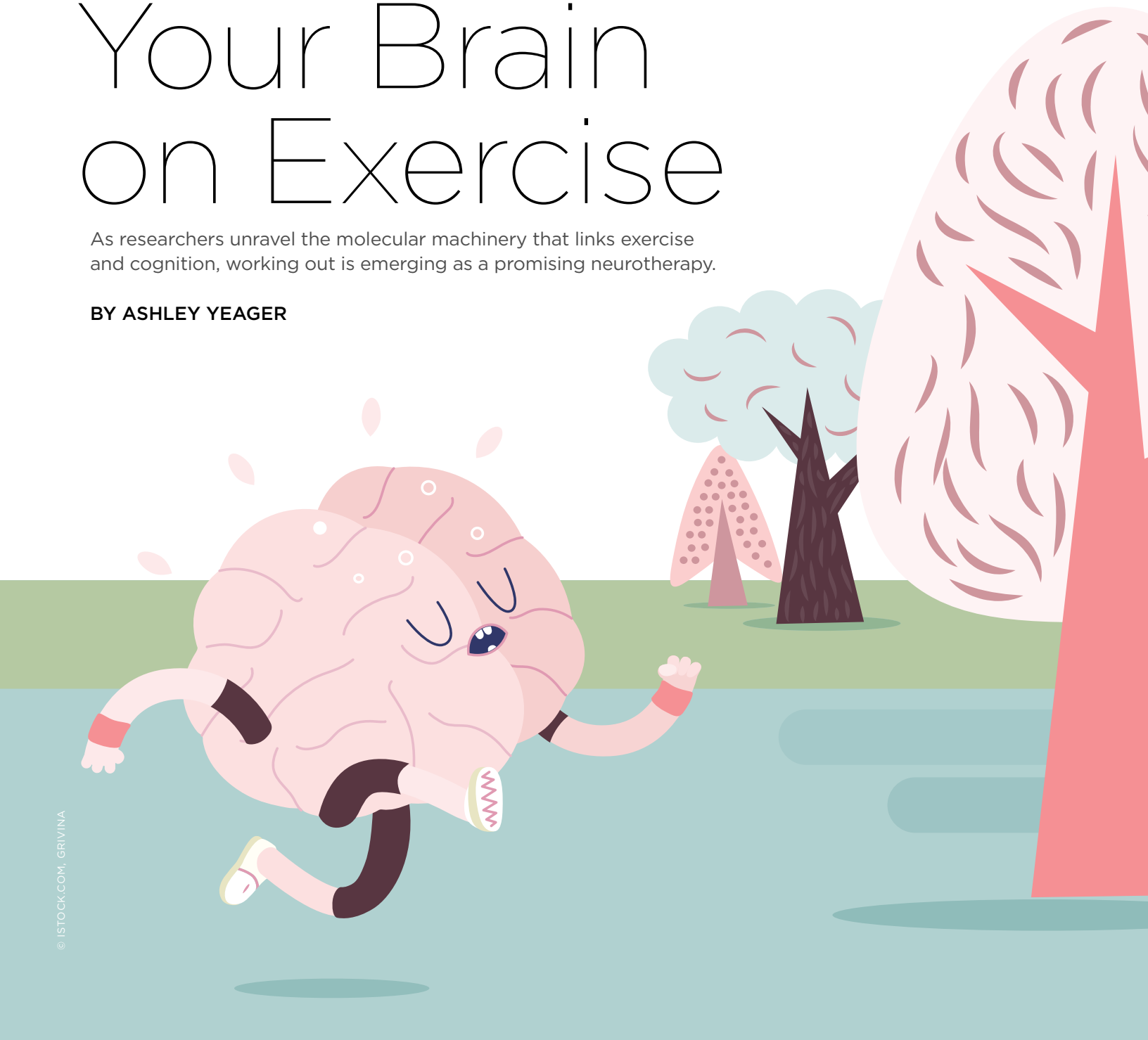
"Intelligence is predictive of a whole host of important things," such as educational attainment, career success, and physical and mental health, Ritchie writes in an email to *The Scientist*, "so it would be extremely useful if we had reliable ways of raising it."



This Is Your Brain on Exercise

As researchers unravel the molecular machinery that links exercise and cognition, working out is emerging as a promising neurotherapy.

BY ASHLEY YEAGER



For an hour a day, five days a week, mice in Hiroshi Maejima's physiology lab at Hokkaido University in Sapporo, Japan, hit the treadmill. The researcher's goal in having the animals follow the exercise routine isn't to measure their muscle mass or endurance. He wants to know how exercise affects their brains.

Researchers have long recognized that exercise sharpens certain cognitive skills. Indeed, Maejima and his colleagues have found that regular physical activity improves mice's ability to distinguish new objects from ones they've seen before. Over the past 20 years, researchers have begun to get at the root of these benefits, with studies pointing to increases in the volume of the hippocampus, development of new neurons, and infiltration of blood vessels into the brain. Now, Maejima and others are starting to home in on the epigenetic mechanisms that drive the neurological changes brought on by physical activity.

In October, Maejima's team reported that the brains of rodents that ran had greater than normal histone acetylation in the hippocampus, the brain region considered the seat of learning and memory.[1] The epigenetic marks resulted in higher expression of *Bdnf*, the gene for brain-derived neurotrophic factor (BDNF). By supporting the growth and maturation of new nerve cells, BDNF is thought to promote brain health, and higher levels of it correlate with improved cognitive performance in mice and humans.

With a wealth of data on the benefits of working out emerging from animal and human studies, clinicians have begun prescribing exercise to patients with neurodegenerative diseases such as Parkinson's and Alzheimer's, as well as to people with other brain disorders, from epilepsy to anxiety. Many clinical trials of exercise interventions for neurodegenerative diseases, depression, and even aging are underway. Promising results could bolster the use of exercise as a neurotherapy.

"No one believes exercise is going to be a magic bullet," says Kirk Erickson, a cognitive psychologist at the University of Pittsburgh. "But that doesn't mean we shouldn't do it."

The body-brain connection

In the late 1990s, then-postdoc Henriette van Praag and other members of Rusty Gage's lab at the Salk Institute for Biological Studies in La Jolla, California, were fascinated with recent findings from the group showing that mice whose cages had toys and running wheels developed more new neurons in the hippocampus, a brain area important for learning and memory, than mice living in less-stimulating enclosures. (See "Lab Toys," *The Scientist*, October 2009.)

Van Praag wanted to identify which element of enriched environments had the greatest influence on the brain. She had some mice learn to swim in a water maze, while others swam in open water, ran on a running wheel, or interacted with several other mice. After 12 days, the development of new neurons was greatest in the group of

mice that ran: they had double the number of new neurons as mice in the maze or water.[2]

In a follow-up study published a few months later, van Praag and her colleagues showed that the neurogenesis sparked by running on the wheel correlated with the mice's ability to remember the location of a hidden platform in a tank of water. The brains of the mice that ran also had greater reorganization of synaptic connections than those from mice that didn't run, suggesting exercise influences plasticity.[3] "The whole line of research into exercise and neurogenesis grew from there," says van Praag, who started jogging regularly after seeing the results.

Over the past two decades, researchers have identified many molecular mechanisms underlying exercise's influence on cognition. Exercise, studies have shown, leads to the release of proteins and other molecules from muscle, fat, and liver tissue that can affect levels of BDNF and other agents that spur neurogenesis, speed new-neuron maturation, promote brain vascularization, and even increase the volume of the hippocampus in humans.

The question then became: How do these factors change the expression of genes in the brain? In 2009, neuroscientist Hans Reul of the University of Bristol and colleagues published one of the first studies to look broadly for epigenetic changes in response to exercise. The team put rats through a stressful challenge, placing them into new cage environments or forcing them to swim in a beaker of water. After the stressful experiences, animals that had run regularly on a wheel had higher levels of histone acetylation across the genome in cells of the dentate gyrus, a part of the hippocampus where neurogenesis occurs. The active animals then acted less stressed than their more sedentary counterparts when reexposed to the stressful environments. The rats that exercised spent less time exploring the new cage or struggling in the water, where they instead floated with their heads above water. The findings suggest that the acetylation induced by the combination of running and stress helped the animals better cope with subsequent stress.[4]

Exercise-induced epigenetic changes "have a remarkable capacity to regulate synaptic and cognitive plasticity," says Fernando Gomez-Pinilla, a neuroscientist at the University of California, Los Angeles, who has led several similar studies.

Since Reul's study, at least two dozen others have reported acetylation and other epigenetic changes that link exercise to the brain in rodents. Moses Chao, a molecular neurobiologist at the New York University School of Medicine, and colleagues recently found that mice that ran frequently on wheels had higher levels of BDNF and of a ketone that's a byproduct of fat metabolism released from the liver. Injecting the ketone into the brains of mice that did not run helped to inhibit histone deacetylases and increased *Bdnf* expression in the hippocampus. The finding shows how molecules can travel through the blood, cross the blood-brain barrier, and activate or inhibit epigenetic markers in the brain.[5]

While some researchers probe the epigenetic connection between exercise and cognitive prowess, others continue to unveil previously unknown links. In 2016, for example, van Praag, now at the Florida Atlantic University Brain Institute, and colleagues found that a protein called cathepsin B, which is secreted by muscle cells during physical activity, was required for exercise to spur neurogenesis in mice. In tissue cultures of adult hippocampal neural progenitor cells, cathepsin B boosted the expression of *Bdnf* and the levels of its protein and enhanced the expression of a gene called *doublecortin* (*DCX*), which encodes a protein needed for neural migration. Cathepsin B knockout mice had no change in neurogenesis following exercise.

Van Praag's team also found that nonhuman primates and humans who ran on treadmills had elevated blood serum levels of cathepsin B after exercising. Following four months of running on the treadmill three days per week for 45 minutes or more, participants drew more-accurate pictures from memory than at the beginning of the study, before they started exercising.[6]

A handful of research groups have now begun to painstakingly look for other molecules released during exercise that could enhance the activity of *Bdnf* and other brain-boosting genes, says van Praag, and it's becoming clear that what's happening in the body affects the brain. "We don't think about that [connection] as much as we should."

> No one believes exercise is going to be a magic bullet. But that doesn't mean we shouldn't do it.
>
> —Kirk Erickson, University of Pittsburgh

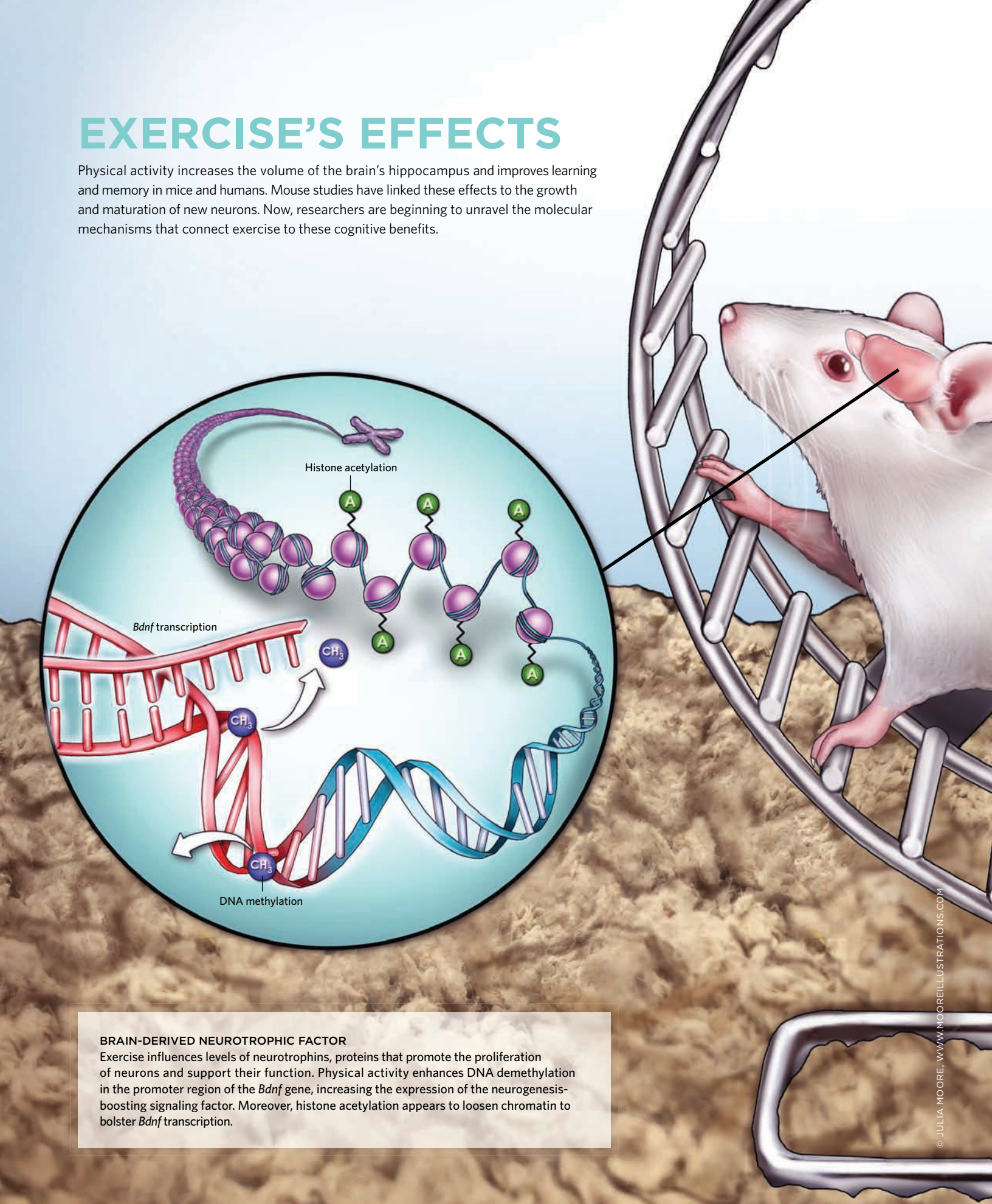
Healing action

Since the 1980s, studies of humans have pointed to a link between exercise and gains in cognitive performance. Understanding this relationship is of particular importance to patients with neurological diseases. University of Southern California neuroscientist Giselle Petzinger has been treating patients with Parkinson's disease for decades and has observed that those who exercise can improve their balance and gait. Such an observation hinted that the brain retains some plasticity after disease symptoms set in, she says, with neural connections forming to support the gains in motor skills.

A few years ago, Petzinger and her colleagues began studying a mouse model of Parkinson's disease. The team found that

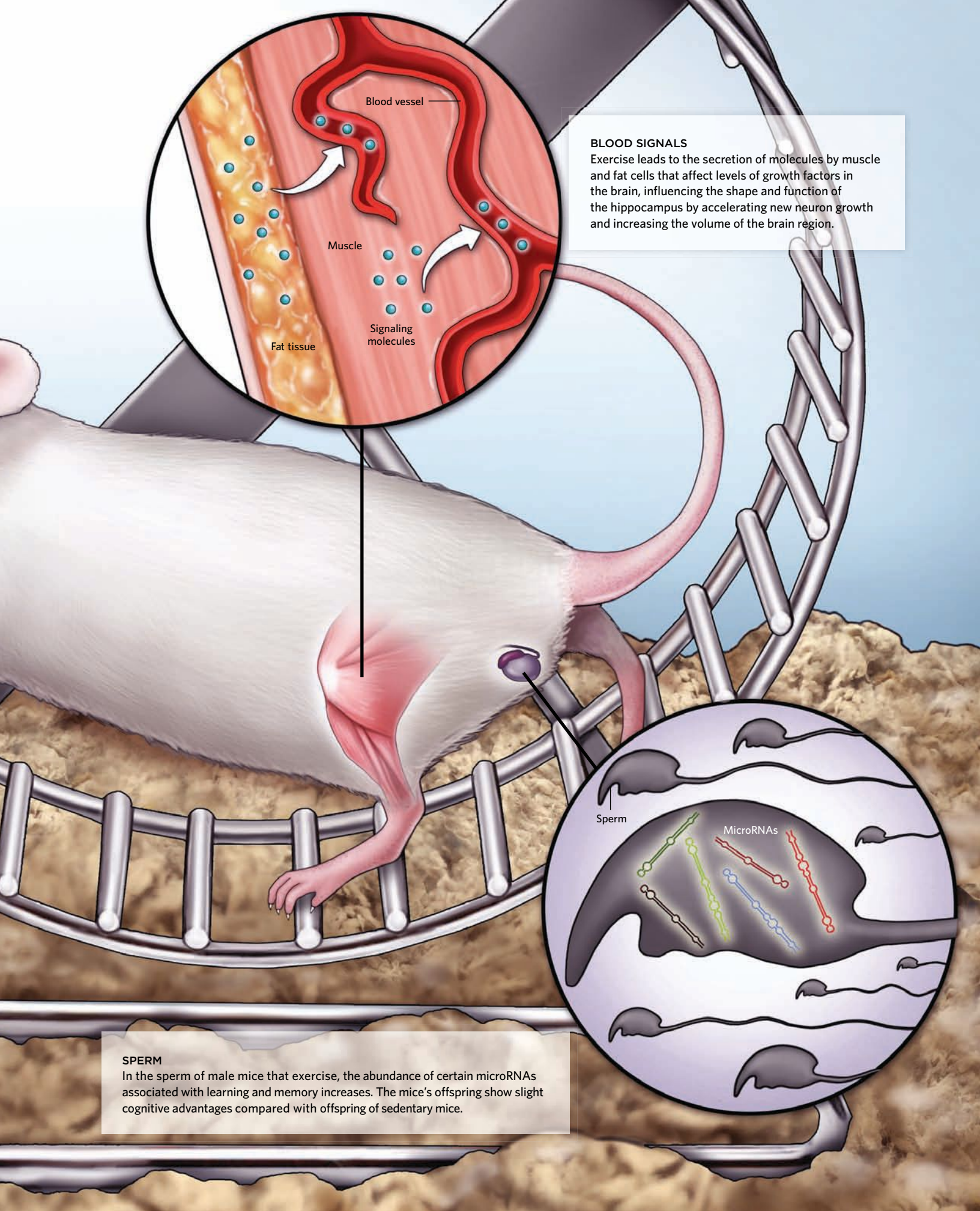
EXERCISE'S EFFECTS

Physical activity increases the volume of the brain's hippocampus and improves learning and memory in mice and humans. Mouse studies have linked these effects to the growth and maturation of new neurons. Now, researchers are beginning to unravel the molecular mechanisms that connect exercise to these cognitive benefits.



BRAIN-DERIVED NEUROTROPHIC FACTOR

Exercise influences levels of neurotrophins, proteins that promote the proliferation of neurons and support their function. Physical activity enhances DNA demethylation in the promoter region of the *Bdnf* gene, increasing the expression of the neurogenesis-boosting signaling factor. Moreover, histone acetylation appears to loosen chromatin to bolster *Bdnf* transcription.



BLOOD SIGNALS
Exercise leads to the secretion of molecules by muscle and fat cells that affect levels of growth factors in the brain, influencing the shape and function of the hippocampus by accelerating new neuron growth and increasing the volume of the brain region.

SPERM
In the sperm of male mice that exercise, the abundance of certain microRNAs associated with learning and memory increases. The mice's offspring show slight cognitive advantages compared with offspring of sedentary mice.

active mice had more dopamine receptors in the basal ganglia, a group of neuronal structures important for movement, learning, and emotion.[7] Levels of dopamine receptors correlate with brain plasticity, and dopamine receptor loss is one of the signature signs of Parkinson's disease. Using a dopamine antagonist as a radioactive tracer, the team found that patients who walked on a treadmill three times per week for eight weeks increased the numbers of dopamine receptors in the basal ganglia.[8]

Petzinger's mouse studies have also revealed other possible mechanisms of exercise's benefits for Parkinson's patients, including the maintenance of dendritic spines, the tiny projections that branch off of nerve cells to receive electrical input from other neurons nearby, and of the synapses along these spines.[9] These effects appear to modify synaptic connectivity within the mice's brains and modify the animals' disease progression, says Petzinger, who is just wrapping up a trial on using exercise to target cognitive impairment in Parkinson's disease.

Prescription exercise may also be beneficial for Alzheimer's patients or individuals at risk of developing the disease. Several studies show that physical activity can counter the

PAYING IT FORWARD

As early as the 1990s, studies started to show indirect links between pregnant women's physical activity and the brains of their gestating babies. For example, a 1996 study showed that at age five, children of moms who exercised regularly during pregnancy performed better on tests of general intelligence and oral language skills than children whose mothers had not exercised much (*J Pediatrics*, 129:856–63). And research backing this association continues to accumulate. In 2016, for instance, one study showed that boys born to physically active mothers had higher scores on math and language tests than boys from sedentary moms (*J Matern Fetal Neonatal Med*, 29:1414–20).

Scientists have long assumed that the exercise-induced changes to offspring are epigenetic in nature, and recent research is beginning to support that hypothesis. One group reported in 2015 that three months of physical exercise changed the DNA methylation patterns of young men's sperm. The tweaks occurred at genes associated with schizophrenia, Parkinson's disease, and other brain disorders (*Epigenomics*, doi: 10.2217/epi.15.29). (See "Ghosts in the Genome," *The Scientist*, December 2015.)

To further investigate exercise-induced changes in gene expression, Anthony Hannan of the Florey Institute of Neuroscience and Mental Health in Victoria, Australia, and colleagues studied the sperm of mice that ran on wheels or performed other physical activities. The team showed that exercise spurred changes in the expression levels of several small RNAs in the germline cells of male mice. It is known that small RNAs packaged into gametes can influence the metabolism of offspring, and possibly also learning and memory. Male mice born to fathers with these changes in their sperm had reduced anxiety levels, leading the authors to conclude that parental exercise can exert a transgenerational effect on offspring's emotional health (*Transl Psychiat*, 7:e1114, 2017).

Earlier this year, André Fischer, an experimental neuropathologist at the German Center for Neurodegenerative Diseases in Göttingen, and his colleagues published one of the most convincing studies showing that the benefits of an enriched environment on the brain can be passed epigenetically from parent to offspring. The team put adult male mice in cages with running wheels and other toys, while a set of their cousins lived in cages without wheels or toys. Synaptic connections increased in the mice in enriched environments, and the team also saw increased connections in the brains of the active mice's offspring—both males and females. The offspring learned a little faster and had a bit better memory recall than mice with parents reared in traditional cages, though the differences were not statistically significant (*Cell Rep*, 23:P546–54, 2018). Analyzing the sperm of the parent mice, Fischer and his colleagues identified two microRNAs—miR212 and miR132, both associated with the neuron development—that appeared to affect cognitive abilities of the active mice's offspring.

It's not yet clear if these findings are translatable to humans, but Fischer and his colleagues write in their study that the results could be important for reproductive medicine. "The idea that . . . training in adulthood provides a cognitive benefit not only to the individual undergoing this procedure, but also to its offspring is fascinating."

Studying exercise's effect on the nervous system could help researchers identify the best and most efficient strategy to maintain brain health as we age.

—Giselle Petzinger, University of Southern California

elevated risk of developing the disease among individuals carrying the *APOE-ε4* allele—the most common gene variant linked with late onset of the disease. And more-recent studies suggest exercise can combat brain deterioration associated with the disease.

In 2018, van Praag, along with researchers from Harvard Medical School, MIT, Massachusetts General Hospital, the Dana-Farber Cancer Institute, and the Salk Institute, published a mouse study that found that neither a neuroprotective drug nor a gene therapy to overproduce WNT3, a protein that has been linked to neurogenesis, reversed signs of dementia. Yet, when the mice were allowed to exercise, their cognitive performance improved. When the team combined the neuroprotective drug with treatments to overexpress the *Bdnf* gene in the brains of mice that didn't exercise, improvements in their cognitive performance matched those of the mice that were given access to a running wheel.[10] The work, van Praag says, may provide avenues toward treating patients with neurodegenerative diseases who are too frail to exercise.

The result also offers support for the 58 clinical trials currently being done on exercise, cognition, and Alzheimer's disease. There are nearly 100 ongoing trials, including Petzinger's, investigating exercise's role in easing Parkinson's symptoms, and hundreds more looking at exercise as an intervention against depression. Some researchers are even testing the effects of exercise on aging.

"An active lifestyle is not going to turn a 70-year-old brain into a 30-year-old brain," says Petzinger. "But studying exercise's effect on the nervous system could help researchers identify the best and most efficient strategy—whether it's activity alone or activity paired with drugs—to maintain brain health as we age." ■

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No Dogs Allowed

Becoming a neuroscientist with a service dog by your side presents numerous challenges. Joey Ramp, who went back to college to study post-traumatic stress disorder, is learning this the hard way.

BY JEF AKST

DORIS DAHL, BECKMAN INSTITUTE, UNIVERSITY OF ILLINOIS

A GOLDEN HELPER: Sampson is a four-year-old golden retriever service dog who aids Joey Ramp as she pursues an undergraduate degree in neuroscience.

In 2006, Joey Ramp suffered 23 broken bones, an injury to her prefrontal cortex, and permanent nerve damage to the left side of her body after she and her horse took a fall. Ramp recalls plunging head first, and then the horse, which she had been training to play polo, rolling on top of her. She fractured her eye socket, cheekbone, and two vertebrae, and broke her jaw and collarbone.

Two years and multiple surgeries later, Ramp's body was restored to the extent that modern medicine would allow, but her injuries meant she could no longer continue her career as a horse trainer. She also faced a bigger problem: severe and lasting damage to her mental health.

In combination with a history of childhood sexual abuse, the accident caused Ramp to develop symptoms that led to a diagnosis of a complex form of post-traumatic stress disorder (PTSD). Shortly after the accident, she began losing periods of time, with no memory of what had happened. She would dissociate from her environment, sometimes rendered unable to communicate, and at times completely losing touch with reality. Ramp, then a single mom in her 40s, became homebound, she says. And with no way to understand what was happening in her brain, she fell into a dark depression that almost ended tragically.

"The day I was going to commit suicide I sat down with my [life] insurance policy in my lap and a gun," she tells *The Scientist*. But a nearby book with a golden retriever on the cover caught her attention. "I picked it up that day and started reading this book on the floor of my office with a gun on my lap."

It was the story of a service dog that had helped a military veteran recover from severe symptoms of PTSD, and it gave her hope. She decided she would look into getting a service dog to help her reintegrate into society and ultimately launch a research career studying PTSD.

"I was like, maybe I can understand," says Ramp. "I was within minutes of taking my own life, and I made the decision to instead try to rebuild one."

Now with her own golden retriever service dog Sampson by her side, the 54-year-old is earning her second bachelor's degree while working in the neuroscience lab of Justin Rhodes at the Beckman Institute for Advanced Science and Technology at the University of Illinois at Urbana-Champaign (U of I). With skills in brain sectioning, immunoassays, and genotyping under her belt, rave reviews from faculty, and an undergraduate thesis in the works, Ramp next wants to earn a PhD.

But her research career faces a major hurdle: at the University of Illinois, Sampson is not permitted into laboratories that study live mammals.

So far, the institution has prevented Ramp from taking a psychology laboratory course involving rat experiments and has kept her out of the Rhodes lab's mouse facilities. "The next hurdle comes with my graduate work," she says. "I [could] be up against the same resistance, and maybe won't be able to follow the graduate direction that I had intended."

Bringing dogs into labs

Wherever Ramp goes, Sampson goes too. In addition to the physical support he provides—helping her up stairs and picking up items off the floor, for example—Sampson is trained to alert Ramp to signs that she is becoming overwhelmed. If she starts rubbing her hands together or tapping her finger, Sampson will get her attention by nudging her leg or hands, and Ramp can assess the situation—and remove herself from it, if necessary.

"He keeps me aware," says Ramp. "If I don't have him, and he doesn't alert [me] to those types of things, I will continue to let those symptoms get worse." In extreme cases, she continues, "I can completely dissociate to a point of not even being aware of my surroundings. And I will continue to function, drive, act, and do everything in a complete state of psychological fugue."

For these reasons, Ramp says, she can't be without Sampson. She first realized that this arrangement would present some challenges in her quest to become a neuroscientist when she started at Parkland College, a two-year community college in Champaign, Illinois, in the fall of 2012. The faculty and administrators had no experience with service animals in the laboratory. After several discussions, they arranged for Ramp and her service dog, then a Labrador retriever named Theo, to attend general chemistry lab courses. Some equipment was moved to ensure that Ramp wouldn't have to crisscross the lab, and Theo had to wear goggles and shoes like the students did. "Everyone involved wanted to see if we could make it work," says Parkland chemistry professor Andrew Holm.

When she started at U of I in 2015, Ramp expected things to be easier. With the institution's 70-year history of disability services, "I didn't foresee a problem,"

I was within minutes of taking my own life, and I made the decision to instead try to rebuild one.

—Joey Ramp, University of Illinois

Ramp's situation raises a difficult question: When should service animals be permitted—or not permitted—in scientific laboratories? As is the case with most difficult questions, the answer is: it depends. Institutions must consider the rights of people with service animals, but also the safety of everyone involved, the integrity of the experiments, and federal regulations for animal care and use.

"It's a very delicate balance," says Patricia Redden, a professor of chemistry at Saint Peter's University in New Jersey who raises service dogs and has served on American Chemical Society committees developing guidance on the admission of service dogs to chemistry labs. "You can't really come out and say, 'No, we absolutely categorically will not allow them.' But on the other hand, you don't want to come out and say, 'Absolutely, you can bring your service dog in.'"

she says. But like the employees at Parkland, the U of I faculty and staff had never fielded such a request, and the university didn't have clear guidelines on admitting service dogs into laboratories.

U of I is not unique in this respect. Universities typically don't have rules regarding service dogs. And policies that do mention service animals generally do not detail procedures for their admission into teaching or research labs, says Jan Novakofski, associate vice chancellor for research compliance at U of I. School policies that mention the prohibition of service animals from the laboratory, such as those of Boston University and Brown University, are vague or allow for exceptions. "There's no clear guidance on how to identify a service dog, more fundamentally, no less where can you take it," says Redden. "It seems to be pretty much a school-by-school decision."

Most of the time, accommodations can be made. In some cases, people who are able to be apart from their service animal might opt for that while in a lab, to ensure that their dog does not come into contact with any harmful agents or other dangers, says Jean Earle, CFO for a nonprofit organization that helps people with disabilities get education and work. Earle's daughter, for example, is raising a service dog puppy while attending the University of Pennsylvania School of Veterinary Medicine, but chooses not to bring the dog into her labs, her mother says.

In other cases, the risks can be mitigated such that service dog teams can feel comfortable entering laboratory environments. In early 2016, after a year of discussions, Ramp's dog Theo became the first service dog ever permitted in a chemistry lab at U of I. The following semester, Sampson accompanied Ramp for a molecular biology techniques course. But a psychology course that she wanted to take involved experiments with live rodents, and Janice Juraska, faculty supervisor for the course, was concerned that the rats would react to Sampson as if he were a predator. As a result, allowing Sampson into the laboratory space with live rodents would violate federal laws protecting research animals, says Robin Kaler, associate chancellor for public affairs at the university.

LAB PARTNER #1: Theo was the first service dog allowed in a chemistry teaching lab at the University of Illinois.

LARA CURRY

For lab exercises involving rats, Juraska and her colleagues said Sampson could stay in a nearby storage room while Ramp attended the session. But if Sampson wasn't going into the lab, Ramp wasn't going in either.

Vague legislation

The US Department of Agriculture's Animal Welfare Act and Animal Welfare Regulations state that separation according to species may be necessary for the humane handling, care, and treatment of animals, while the Guide for the Care and Use of Laboratory Animals, put out by the National Research Council of the National Academies, recommends the separation of species "to prevent interspecies disease transmission and to eliminate the potential for anxiety and physiologic and behavioral changes due to interspecies conflict."

These laws don't address the presence of service animals in the laboratory specifically, and the National Institutes of Health's Office of Extramural Research notes that there are many possible exceptions to the recommendation that different species be housed separately. But when it comes to service dogs, "generally they should not be brought into an animal facility or laboratory to ensure biosecurity," according to a statement from the office emailed to *The Scientist*.

Kaler says the university staff's hands are tied by the federal regulations. And while each request is evaluated individually, and thus there is not a university-wide ban per se, Kaler says, "we would not allow service animals in labs with live mammals."

In addition to animal welfare regulations, a university must also take into consideration the Americans with Disabilities Act (ADA) and section 504 of the Rehabilitation Act. Both laws protect the right of people with service animals to enter areas that are open to the public. Yet neither the Animal Welfare Act nor the NRC Guide provides rules regarding the admission of service animals to teaching and research labs. "That's where it's become so gray," says Redden. "The law is not totally clear on it."

When enforcing these federal regulations on campus, there are two relevant exceptions to the laws' protection, says L. Scott Lissner, the ADA and 504 compliance officer at Ohio State University. The first is if there is a direct threat to the health and safety of others. "The very commonsense rule of thumb . . . is if people have to suit up to go into the lab, then usually the dog can't go in." For some labs, such as those associated with chemistry and biology courses, protective gear for the dog may suffice. Labs that maintain sterile facilities or contain hazardous pathogens, on the other hand, are typically off limits.

The second exception is if there is evidence that the animal's presence would "fundamentally alter the nature of the work in the lab that was being done," Lissner continues. "If we couldn't properly do the experiment, then we couldn't teach the class, or we couldn't do the research."

The nature of these rules necessitates universities' case-by-case approach to requests to admit service dogs to the lab. "You just take every single situation and assess it carefully," says Earle, who has advocated for access for her older daughter's service dog to environments such as hospital rooms, so they could be together during recovery from surgery. "[The appropriate solution] would vary with every single lab, and every single topic; it could even vary with the particular curriculum and goals for that day."

When it came to Ramp's request to bring Sampson into the psych lab, Juraska had safety concerns. She thought that the dog risked exchanging pathogens with the rats, but more worrisome, his presence might affect the rats' behavior. Becoming anxious or fearful, the rats might get agitated and bite a student, she says. Even a less extreme reaction could disrupt the experiments the students were running, and the rats could suffer in a way that went against animal welfare guidelines. "Wolves, and by extension dogs, are known predators, and there is research [showing] that their presence can cause anxiety and aggression in a prey species," Juraska tells *The Scientist* in a written statement.

Ramp isn't satisfied with the university's justification. She's been told by veterinarians that the risk of pathogen transmission between service animals and lab animals is very low, and she's skeptical that Sampson, who has been specifically trained for the lab environment, will stress the rodents any more than a classroom full of students. But she has not been able to convince U of I. "It really became lots of resistance and no problem solving," she says. "And I've been fighting that issue for the last year and half now."

> There's no clear guidance on how to identify a service dog, more fundamentally, no less where can you take it.
>
> —Patricia Redden, Saint Peter's University

Accusations of discrimination

Although there is some evidence that wild rats respond to dogs as predators, Ramp could not find compelling research on the effect of dogs on lab rats. "These are not wild rodents," Rhodes says. "They're domesticated and have no experience with dogs." But there doesn't seem to be any research addressing this question.

Recognizing this problem, Ramp applied for and received a $50,000 grant from an independent donor through the university's Disability Resources and Educational Services (DRES) for a two-year study to explore this question. She joined

LAB PARTNER #2: Sampson was the first service dog to enter a University of Illinois biology teaching lab, a molecular and physiology research lab, and a behavioral genetics and neuroscience research lab.

THOMPSON MCCLELLAN PHOTOGRAPHY

Rhodes's lab and enlisted his help in writing a protocol for the study to submit to the Institutional Animal Care and Use Committee (IACUC).

The researchers proposed an experiment in which Ramp and Sampson would enter a room housing mice, and Sampson would lie on a mat. Ramp would record for ultrasonic vocalizations and assess the animals' anxiety through behavioral tests. These results—along with levels of blood corticosterone—would be compared with the outcomes of the same experiments conducted by Ramp without Sampson present. (Ramp says she would work to ensure that the environment would be free of possible triggers and that she'd have help from Sampson immediately if she started to have symptoms. "The experiments would take place in short 10- to 15-minute increments so that I would only be separated from him for a short period," Ramp explains.)

The study could provide data to guide appropriate policies regarding service animals in labs with live animals, Ramps says, and either give her confidence to pursue research that involves rodents or push her in a different direction. But to her and Rhodes's surprise, the IACUC rejected the protocol—twice.

The first rejection, from last December, simply cites "insufficient justification for the use of live vertebrate animals (mice)."

SERVICE DOGS IN THE LAB

When a student with a service animal chooses to take a laboratory course, she should contact the institution's disability services office to help arrange accommodations. In consultation with the faculty and staff in charge of the lab sessions, the case worker and student can devise a plan to ensure the safety of everyone involved.

LABORATORY ACCOMMODATIONS FOR SERVICE DOGS

Consider outfitting animals with personal protective equipment (googles, boots, lab coat)

Develop in-class protocols (e.g., the lab manager can supply the student's bench area with equipment and reagents before class starts; service dog teams should use communal equipment first or last)

Ensure easy access to an exit and safety shower

Find an appropriate lab partner (who is willing to help with steps that may not be easy or possible for a student with a service dog)

Choose an appropriate lab bench position for the student/dog team (back corner where dog can lay directly behind student out of traffic)

TRAINING A SERVICE DOG FOR A LABORATORY ENVIRONMENT

- Willing to wear boots, goggles, and other protective gear
- Trained to lie on a mat with rubber backing for extended periods
- Trained to NOT automatically retrieve items off the ground
- Conditioned for emergency situations
- Willing to stand under a safety shower
- Trained to find an exit

Assuming the committee had misunderstood their proposal, Ramp and Rhodes had multiple meetings with Pat Malik, the director of DRES, and also spoke with IACUC head Josh Gulley. Rhodes then went before the entire committee to explain the scientific rationale and assure them that the experiment would be "pretty much innocuous" for the mice involved—IACUC's main concern being for the welfare of the animals and the scientific justification for any harm they might endure. But again in March, the committee denied the request.

"I didn't understand why," Rhodes says. "I'm still surprised."

The second rejection letter listed four main objections, including concerns related to the study's purpose, the lack of a hypothesis, and the possible biosecurity risk. But none of the arguments "held any water," Rhodes insists. "It's the kind of experience where you think you're going crazy. . . . There doesn't seem to be any legitimate reason why they would block us."

Rhodes has never had another protocol rejected by the IACUC at U of I—and he's written a dozen or more—nor does he know anyone who has had a protocol rejected. B. Taylor Bennett, senior scientific advisor at the National Association for Biomedical Research, says that IACUCs "rarely reject a protocol outright unless it involves projects that they are not equipped to support, or where the biosecurity of the animals would be an issue."

Gulley says he is not able to comment on specific IACUC submissions. Juraska, who has not read the protocol, has concerns about Ramp conducting the experiment herself. "That would not be correct scientific practice," she writes to *The Scientist*. "A disinterested person should do the actual experiment, one who does not have a stake in the outcome and does not even know whether the dog is in the room."

ALWAYS THERE: Sampson accompanies Ramp to a ceremony for a Fred S. Bailey scholarship she was awarded.

COURTESY OF JOEY RAMP

Ramp says she suspects that Sampson's ban from the psych lab and the IACUC's rejection of their proposal are related, and stem from prejudice against people with service dogs. In May, she filed a complaint with the US Department of Education's Office for Civil Rights (OCR) alleging discrimination by the university, the IACUC committee, and Juraska.

"We think that the entire response of the university reflects discrimination and in some respects may reflect retaliation for her efforts . . . to bring her dog in [to the lab]," says Ramp's lawyer Matt Cohen, who specializes in disability rights.

The university declined to participate in mediation, Cohen says, and the OCR has initiated an investigation on the IACUC's rejection. (The agency is not investigating Sampson's ban from the psychology lab course because the complaint was filed more than 180 days after the incident.) The university would not confirm or deny the complaint or investigation.

> It's hard to come up with hard and fast rules that are simple enough for everyone to follow and still are acceptable legally.
>
> —Jean Earle, ECLC of New Jersey

Ramp paves the way

Regardless of the outcome of her legal case, Ramp is hoping that her story will motivate the development of better guidelines for making accommodations for people with service dogs in the sciences, whether in laboratory classes or research facilities with animals.

Service animals are becoming more common—the number of active guide, hearing, and service dogs in North America, Australia, New Zealand, and Asia nearly doubled between 2009 and 2017, from 10,769 to 19,144, says Chris Diefenthaler, operations administrator at Assistance Dogs International. Thus, this is an issue that universities are likely to face more frequently.

According to Kaler, U of I is already developing an update to its policy on animals on campus. Administrators have been working for a year on a version that will specifically mention labs. The new policy has been reviewed by the university's legal team and has begun the process of review by the university. Students, faculty, and other staff will have the opportu-

nity to comment before it is added to the Campus Administrative Manual, she says.

Several institutions have already published new policies on having animals on campus in the last several years, and many more are on the way, says Novakofski. But given the rare and diverse nature of the requests to bring service dogs into the laboratory, it's "hard to come up with hard and fast rules that are simple enough for everyone to follow and still are acceptable legally," Earle reiterates. More important than concrete policies on service dogs in the lab, she adds, are guidelines on what to consider when making the decision and protocols for making accommodations when appropriate.

In March, Redden and Christopher Sweet at Cornell University's Institute on Employment and Disability published a chapter in an ACS Symposium Series book on admitting service dogs to chemistry labs. And Ramp has put together a template based on her experiences with Theo and Sampson. (See infographic on page 47.) At Parkland College, her efforts are already making a difference, says Parkland's Holm. The campus has since made accommodations for service animals to accompany their handlers to the gym and to a cadaver lab, and there is currently a student with a service dog taking the same intro chemistry lab that Ramp took with Theo. "Her pioneering—it's paying off," Holm says.

A career in research may not be in the cards for Ramp, though. While she awaits the OCR's decision, she is considering her future. If she is unable to get IACUC approval for her study, she will lose her funding, and she will not have data to know whether she can conduct the mouse experiments she'd envisioned for her graduate research. One back-up plan on the table is attending law school. If science doesn't work out, Ramp hopes that a law degree could allow her to help other individuals with service dogs navigate the legal system, and to change policies that discourage these people from pursuing an education in STEM.

"When a barrier becomes immovable then how do you maneuver around it?" says Ramp. "Perhaps this could be the way I could open doors for other scientists who follow me." ■

SERVICE DOG POSES HURDLES FOR PRE-VET STUDENT

Since she was four years old, Sydney Sheets has wanted to be a veterinarian. She joined 4H when she was nine and began training and showing dogs. Beginning in fifth grade, she volunteered at a local vet clinic, even scrubbing in for surgeries. And when she started college in 2015, she chose Texas A&M University because of its renowned veterinary medicine program.

But at age 16, Sheets learned she had type 1 diabetes. Rocked by the diagnosis, she focused on something a nurse at the hospital had told her—she could get a service dog. She found her puppy, a Belgian tervuren she named HALO, through a certified breeder, and with the help of her dad and 4H leaders, trained him to alert her to dangerous swings in her blood sugar levels. By her sophomore year of college, Sheets didn't go anywhere without him.

Like Joey Ramp, Sheets is running into problems pursuing her dream job and the education that would make it a reality with a service dog by her side. Both at Texas A&M and at Tacoma Community College outside of Seattle, where she took classes during the summer, HALO attended biology and chemistry labs with Sheets. He even followed along to a course on reproduction in farm animals, which included palpating a cow to check to see if it was pregnant. The professors, TAs, and administrators at the school helped make the necessary accommodations to allow HALO to continue monitoring Sheets while she participated in such activities.

But when she enrolled in an animal science research class that involved field trips to the Texas A&M's horse, sheep, pig, and cattle facilities, the professor, Courtney Daigle, told Sheets that HALO was not allowed. Sheets filed a complaint with the school, which found that the professor had not been in compliance with the ADA, Sheets says. Still, she withdrew from the class, later switched her major to sociology, and is now rethinking her career direction. "[The incident] just kind of sucked a lot of the joy out of what I was doing," says Sheets, who is set to graduate in December 2019 and hopes to pursue a PhD in psychology. The university could not confirm or deny the existence of the complaint or the experiences of an individual student; Daigle did not respond to requests for comment before deadline.

Sheets's experience, like Ramp's, illustrates the challenges of bringing a service dog into the sciences. "It's really discouraging," says Sheets. "A lot of people are not going to do STEM just because some battles aren't necessarily worth fighting that hard."

"For her to say I'm done [with veterinary medicine] was a little bit heartbreaking for all of us," says Sydney's mom Karin Sheets, "because this has always been her dream."

COURTESY OF SYDNEY SHEETS

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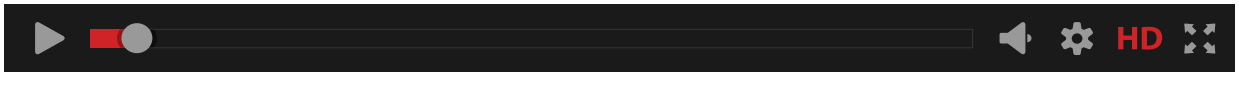

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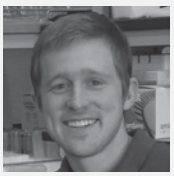

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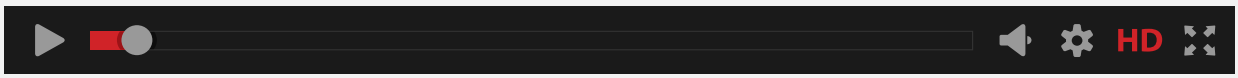


The Literature

NEUROSCIENCE

Disrupting the Flow

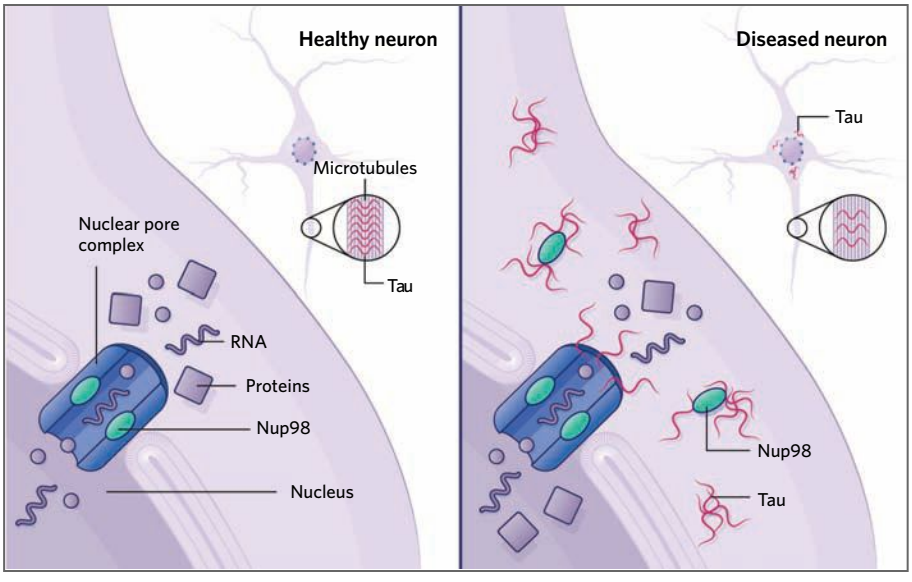
THE PAPER

B. Eftekharzadeh et al., "Tau protein disrupts nucleocytoplasmic transport in Alzheimer's disease," *Neuron*, 99:925–40.e7, 2018.

Dotted along the edges of neuronal cells' nuclei are protein complexes that act like border agents, carefully monitoring the RNAs and proteins that move into and out of the command center of the cell. Disruptions at the border—such as an improper flux of certain proteins—can cause problems for the cell and may underlie Alzheimer's disease (AD) and other neurological conditions.

Researchers have previously linked defects in the gatekeeping protein structures—called nuclear pore complexes—with aging, amyotrophic lateral sclerosis, and other neurological diseases. But a new study "demonstrates that nuclear pore impairment seen in AD is likely a primary target of the disease, rather than a nonspecific defect," Hong Joo Kim, a cell and molecular biologist at St. Jude Children's Research Hospital who was not involved in the work, tells *The Scientist*.

Past studies have shown that nuclear pore impairment is related to rogue tau proteins moving from the microtubules in the axons of neurons to the cytoplasm. Clumping of the tau proteins has long been associated with AD. Bradley Hyman, a neurologist at Massachusetts General Hospital and Harvard Medical School, and colleagues wanted to understand exactly how tau is involved in neuronal cell damage. By staining and imaging tau and other proteins in the brains of humans with and without the disease and in wildtype mice and transgenic mice expressing mutant human tau, the team found that tau interacts directly with Nup98, a building block of nuclear pore complexes. In diseased brains, some Nup98 appears to be misdirected to the cytoplasm. In addition, experiments in cultured cells in which Nup98 was placed in the cell cytoplasm showed it helped to enhance tau aggregation there.



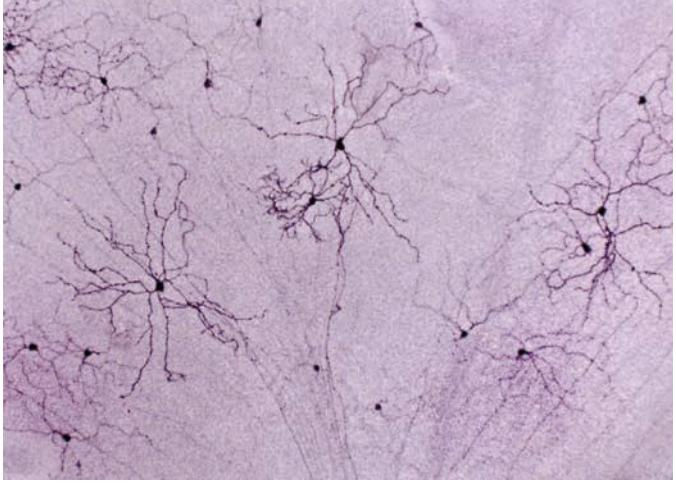
TRAFFIC: In healthy neurons (left), tau protein is confined to microtubules. But in Alzheimer's, tau aggregates disrupt the flow of proteins and RNA into and out of the nucleus of neuronal cells and also draw the protein into the cytoplasm (right). Nup98's presence in the cytoplasm leads to continued aggregation of tau into the neurofibrillary tangles that serve as a signature of Alzheimer's disease.

"The neatest part of the research is that we may have found a mechanism of toxicity for tau," Hyman says. Tau appears to draw Nup98 out of the nuclear pore complex, disrupting its operations, and then Nup98 helps tau aggregate, leading to cell death.

Tau aggregates did seem to alter nucleocytoplasmic transport, Roy Parker, a biochemist at the University of Colorado Boulder who coauthored a perspective accompanying the new paper, writes in an email to *The Scientist*. However, "I was not convinced that the interaction with Nup98 was the fundamental mechanism behind this effect," he says. Many protein aggregates disturb movement between the nucleus and cytoplasm, he explains, but not all of the mechanisms are well understood, and others may be at work in Alzheimer's disease.

"An important question that remains to be answered is whether the interaction of disease-associated proteins with Nup98 is specifically important to initiate the pathogenesis," Kim says. It will also be interesting, she adds, to find out whether other disease-related proteins directly interact with components of the nuclear pore complex. Still, the new study, she notes, does suggest drugs reducing protein aggregation or preventing tau aggregates from interacting with nucleoporins could provide some benefit in AD and other neurodegenerative diseases.

—Ashley Yeager



PROJECTION: Intrinsically photosensitive retinal ganglion cells help transmit light signals from the retina to mood-regulating neural circuits.

LIT UP: Suppressing activity in the amygdala (red) reduces fear.

NEUROSCIENCE

Mood Lighting

THE PAPER

D.C. Fernandez et al., "Light affects mood and learning through distinct retina-brain pathways," *Cell*, 175:71–84.e18, 2018.

SEASONAL BLUES

Depressive feelings associated with fewer hours of daylight in winter were once considered an indirect consequence of circadian rhythm disruption. But in 2012, chronobiologist Samer Hattar, then of Johns Hopkins University, and colleagues showed that light can boost mood scores—along with learning ability—in mice, even when sleep and circadian rhythms are unperturbed.

THE THIRD CELL

To understand these effects, the researchers looked at recently discovered photoreceptors known as intrinsically photosensitive retinal ganglion cells (ipRGCs), which unlike rods and cones play no role in image formation. "Anatomical data suggested that [the] cells can directly influence several brain areas involved in mood and learning functions," study coauthor Diego Fernandez of the National Institute of Mental Health, where Hattar now works, writes in an email.

FORK IN THE ROAD

Unexpectedly, transgenic mice with different populations of ipRGCs ablated revealed two independent pathways mediating mood and learning. One set of ipRGCs projected to the suprachiasmatic nucleus, a brain region associated with circadian function—although rhythms were unaffected in the animals. That pathway mediated light's effects on learning, while cells projecting to the perihabenular nucleus in the thalmus regulated mood. "We were stunned that they are completely dissociable," Hattar says.

OUT OF THE DARK

The results further support the circadian-clock independence of some of light's effects, and could illuminate the mechanisms behind neuropsychiatric disorders associated with certain light conditions, says Lily Yan, a neuropsychologist at Michigan State University. Hattar's team is now keen to understand more about light's effects, he says. "Why should light enhance your mood?"

—Catherine Offord

NEUROSCIENCE

Overcoming Fear

THE PAPER

L.D. de Voogd et al., "Eye-movement intervention enhances extinction via amygdala deactivation," *J Neurosci*, 38:8694–706, 2018.

EYEING THE PROBLEMS

Some psychotherapists coach patients to recall traumatic memories as they make back-and-forth eye movements, tracking the therapist's hand. The procedure, eye movement desensitization and reprocessing (EMDR), helps lessen the power of those memories, but how it works "has been kind of unknown," says psychologist Joseph Dunsmoor of the University of Texas at Austin.

ENHANCING EXTINCTION

Lycia de Voogd of Radboud University in the Netherlands and her colleagues sought to integrate EMDR and a form of conditioning known as fear extinction, a way of lessening fear through repeated exposure to a stimulus. They gave 24 healthy subjects electric shocks to their fingers as the participants looked at blocks of color on a screen. The next day, the participants simply looked at the blocks, with or without tracking a moving dot with their eyes for 10 seconds. On the third day, the researchers reapplied the shock to subjects as they looked at the color blocks again in order to reinstate the fear response.

SETTLE DOWN

EMDR in tandem with fear extinction dampened skin conductance, a measure of fear, more than extinction alone. Additionally, fMRI scans of participants revealed that reduced fear recovery corresponded with less activation in the fear-processing amygdala. Both a working memory task, which involved keeping track of a number sequence, and guided eye movements independently tamped down activity in the amygdala while activating brain pathways involved in controlling emotion.

LOOKING FURTHER

Dunsmoor, who was not involved in the study, notes that knowing the mechanism underlying EMDR could help identify other techniques to help patients deal with trauma.

—Sukanya Charuchandra

PROFILE

Genetic Neurologist

Driven to find ways to help patients with rare nervous system disorders, Huda Zoghbi has spent her career understanding the genetic and molecular basis of neurodevelopment.

BY ANNA AZVOLINSKY

In 1976, Huda Zoghbi (then Huda El-Hibri) was an eager first-year medical student at the American University of Beirut, Lebanon, her hometown. Halfway through that year, a civil war broke out. "Bombs were falling all around the medical campus," the neuroscientist recalls. "I couldn't commute 500 feet, let alone the two miles it took me to get home every day." She and the other 62 students in her class decided that they, along with their professors, would live on campus—mostly underground, in double-walled rooms—to finish the school year.

Although the medical school was considered a safe zone, as both warring factions would send their wounded there for care, an occasional bullet or piece of shrapnel still pierced the campus. One afternoon, Huda had ventured out for a walk on campus with her boyfriend, William Zoghbi, a fellow medical student. They were holding hands and for no particular reason let go. In those few seconds, a bullet flew between them. Neither was hurt, but the young couple realized in an instant how close and serious the war really was.

Later, shrapnel wounded Huda's younger brother while he was walking home from high school, so their parents decided to send them and another sibling to Texas, where their oldest sister was a professor of philosophy. The move was supposed to be temporary. But when the 1977 school year was to start in Lebanon, the civil war was still raging, and neither Huda nor her siblings could return home.

She was devastated that she could not continue medical school, and she worried about her parents, living in Beirut surrounded by war. But Huda was also resolute in continuing her education. She found a medical school, Meharry Medical College in Nashville, Tennessee, that allowed her to join even though its academic year had already begun.

Despite the tenuousness of her situation, Huda made do. She excelled academically. By this time, William had joined her for medical school in Nashville, and after graduation, they moved to Houston, Texas. There, Huda began a residency in pediatrics at the Baylor College of Medicine in 1979. She was initially fascinated by cardiology, but a rotation in neurology opened her eyes to the ways that neurodevelopment can go awry during childhood. "I kept being drawn back to these patients, thinking how fascinating the brain is and how as clinicians, we had to use logic to figure out which part of the brain's anatomy has a problem and is driving the symptoms," she says. She switched her specialty. She and William, a cardiologist, married soon after.

Since then, Huda Zoghbi has uncovered the molecular mechanisms of normal neurodevelopment and neurodegeneration by probing the complexities of rare neurological diseases, including Rett syndrome and spinocerebellar ataxia.

LITERATURE, THEN RESEARCH

Zoghbi was born in Beirut in 1954. Her mother raised her and her siblings while her father ran their family's olive oil–based natural soap company. She recalls a simple and happy childhood by the Mediterranean Sea, playing outdoors, studying, and reading. She devoured Jane Austen, Shakespeare, and Fyodor Dostoevsky, as well as Arabic literature. She wanted to be a writer, but her mother convinced her that, with her excellent grades in math and the sciences, she should plan to go to medical school. Zoghbi entered the American University of Beirut as an undergraduate in 1973, majoring in biology.

"My love of literature has helped my research career," she says. "My colleagues tell me that when I give scientific talks or write a paper, I always tell a story. So I ended up channeling my passion for writing into my science career."

After her pediatric residency at Baylor, Zoghbi stayed at the Houston-based institution, starting a pediatric neurology fellowship in 1982. She was frustrated by the fact that medical science could only ease the symptoms of the many children she worked with who suffered from untreatable neurological disorders. It was then that a patient caught her attention: a girl with Rett syndrome, a rare, poorly characterized disorder that leads to severe learning disability and motor impairments, including ataxia—balance and coordination problems—loss of speech, seizures, and some autism-like behaviors, most distinctively repetitive hand-wringing movements.

"The children are born normal, acquire milestones, and then gradually lose them," she says. "I saw two Rett patients in the same week, and this is a rare disease affecting about 1 in 10,000 girls." In the scientific literature, there was no reporting of Rett patients in the US, so Zoghbi set out to find additional individuals with the disease. She studied six of them to understand the pathogenesis of the disorder and found that the girls had decreased circulating metabolites of key neurotransmitters, norepinephrine and dopamine in particular.

Those results, and Zoghbi's work over the next few years, helped Baylor become a major Rett syndrome referral center. The disorder mostly afflicts female offspring of healthy parents, making it 99.5 percent sporadic from an epidemiological stand-

HUDA ZOGHBI

Professor, Baylor College of Medicine, Houston, Texas
Founding director of the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital
Howard Hughes Medical Institute investigator
National Academy of Sciences member
Vilcek Prize in Biomedical Science, 2009
The Shaw Prize Laureate in Life Science and Medicine, The Shaw Prize Foundation, Hong Kong, 2016
2017 Breakthrough Prize in Life Sciences
Canada Gairdner International Award, 2017

Greatest Hits

- Discovered the X-linked gene, *MECP2*, encoding a methyl-CpG-binding protein, a mutation in which results in Rett syndrome, a rare neurodevelopmental disorder that almost exclusively affects girls.
- Created a mouse model of Rett syndrome and uncovered the cell type–specific requirements for *Mecp2* in the brain.
- Identified that low expression of *Mecp2* results in Rett-like features, while overexpression of the gene results in a different neurodevelopmental disorder that includes autism-like symptoms.
- Along with the lab of Harry Orr, discovered the gene mutated in spinocerebellar ataxia
- Identified the *Atoh1* gene, which encodes a transcription factor essential for development of inner ear hair cells and the Merkel cells of mammalian skin for the light-touch response, to discriminate shapes and textures.

point. Still, Zoghbi hypothesized that Rett syndrome disrupts a specific biological process and has a genetic basis, because the symptoms are consistent from patient to patient. She wanted to do additional Rett syndrome research, but she had no prior lab experience. So she decided to do a postdoc and zeroed in on the lab of Arthur Beaudet, also at Baylor, who studied genetic metabolic disorders.

Zoghbi laid out her case for pursuing the genetic basis of Rett, including her access to more than 100 patients. Beaudet told her that, although he would take her on as a postdoc, finding a genetic cause for the rare disorder was too tall an order and that she should find a more tractable project. She took the advice and wrote a proposal for the National Institutes of Health Mentored Clinical Scientist Research Career Development Award, also called the K08, which provides five years of support for a clinical researcher who aims to establish their own laboratory. Zoghbi suggested studying spinocerebellar ataxia (SCA) type 1, an autosomal dominant, usually adult-onset neurodegenerative disease for which a causative genetic mutation was not yet known.

"I wrote the proposal before I had any publications, when I had no clue how to do anything in the lab. But I had determination, and a good mentor and scientific question," she says, noting that the award, which Zoghbi won in 1985, was a lucky break for her career. "I had five years of funding, and I told myself that I will give science these five years and won't quit before then."

By this time, she and William had a toddler and a four-month-old infant. She took graduate courses, learning molecular biology and genetic linkage mapping.

After three years, Zoghbi finally made progress: she approximately mapped the SCA locus to a region of human chromosome 6.

THE BIOLOGY OF RETT SYNDROME

Beaudet eventually advised Zoghbi to apply for funding to start her own laboratory. In 1988, she became an assistant professor at Baylor. Deciding not to heed the advice of Beaudet and other colleagues, Zoghbi returned to studying Rett syndrome, convinced that she could map the causative gene, which she suspected was on the X chromosome. Over the next 10 years, she and her lab members began to collect tissue samples from families with two affected sisters, systematically comparing each of their X chromosome genes. This project helped Zoghbi's lab, in 1992, to identify a region of the X chromosome that har-

bored the likely mutation. Then, in 1999, Zoghbi and her collaborators identified the exact gene, *MECP2*, which is mutated in Rett syndrome sufferers. The researchers showed that Rett was indeed an X-linked dominant disorder, meaning that just one mutated copy of *MECP2*, which normally encodes a methyl-CpG-binding protein, was enough to cause the disorder.

There are three things that for me were crucial in my career: mentors that believed in me, a supportive family, and the sparse rewards of positive data.

Then, in a mouse model of Rett's syndrome that the lab developed, the team confirmed, in 2009, that a mutation in *Mecp2*, the mouse homolog of *MECP2*, results in a reduction of serotonin and other neurotransmitters, as Zoghbi had first observed in 1983 and reported in 1985. The lab also found that such a mutation partially disables excitatory neurons, and confirmed that practically all brain cells require the protein encoded by the gene.

This and other mouse models also taught the team that while eliminating the function of *Mecp2* in just 50 percent of brain cells results in Rett syndrome symptoms, overexpression also caused a neurological disorder. Zoghbi and her lab mates supported the validity of their findings in mice by reporting that in human male cases, patients had an increased number of copies of the *MECP2* gene, while other labs reported on the rare female cases. Those extra copies increased protein levels, leading to neurodevelopmental delays. "From our mouse models, we learned that the brain is really sensitive to the dose of this gene, which must be tightly regulated. Slightly less protein and slightly more protein can lead to disease," Zoghbi explains.

Recently, in collaboration with a biotechnology company, Zoghbi's lab has developed a potential therapy for decreasing *MECP2* expression. The team is using an antisense oligonucleotide that binds *MECP2* RNA and prevents its translation into protein, and is testing the oligonucleotide in animal models to identify the appropriate dosage to dial back *MECP2* expression just enough—"too little will cause Rett-like problems," Zoghbi says.

"When I started working on Rett, most researchers didn't think that sporadic disorders could be genetic, but here we found a disease that is genetic but a result of a de novo, not an inherited, mutation," she explains. "This has opened up the search for other genetic forms of disabilities that are sporadic but still caused by a genetic defect."

TACKLING OTHER NEUROLOGICAL DISEASES

In parallel to the Rett syndrome studies, Zoghbi's lab also continued to work on SCA1. "With Rett syndrome, had we been waiting for a discovery for 16 years, I would have killed my career," she says.

When she started her lab, Zoghbi contacted Harry Orr, a University of Minnesota researcher who was also working on the genetics of SCA1. The two labs collaborated, identifying the mutation that caused the disease. First, they found the probable region of chromosome 6 where the *SCA* gene sits. Then, on the same spring day in 1993, the two groups realized that they had found the exact locus on chromosome 6: an unstable trinucleotide CAG repeat. "That was a sweet and exciting moment because both of our labs had been working on this for years," Zoghbi says.

Zoghbi's lab went on to create a mouse model for SCA1 that showed that certain neurons are more sensitive to mutant ataxin-1. "From this rare disease, we've learned a lot about factors that drive degeneration in neurons, which helps us to think about more common neurodegenerative diseases like Parkinson's and Alzheimer's," Zoghbi says.

In the midst of these two major lab projects, Zoghbi says that she was craving a fun, basic-science project that did not carry the emotional weight of studying human diseases. Her Baylor colleague, a neurobiologist and fruit fly geneticist, Hugo Bellen, helped her zero in on *atonal*, which encodes a transcription factor and is required for the development of the peripheral nervous system. When mutated, atonal results in deaf and uncoordinated flies. Zoghbi's lab began to search for the homologous gene in mice. In 1999, they discovered it—it's called *Math1* (*or Atoh1*) and is critical for the genesis of hair cells in the cochlea and vestibular system. And in 2009, they found that knocking out *Math1* in mouse skin cells results in the loss of Merkel cells, part of the peripheral nervous system. These cells, the team found, are essential for discriminating among shapes and textures during touch, the so-called light-touch response. That same year, the lab also found that deleting the *Math1* gene could prevent medulloblastoma, a type of brain tumor.

"Even what I considered as fun projects have revealed themselves to be medically relevant," Zoghbi says.

BUILDING SCIENCE CONFIDENCE

While successful now, Zoghbi says, she had no confidence that she would be successful when she started out. She just had a lot of determination. "There are three things that for me were crucial in my career: mentors that believed in me, a supportive family, and the sparse rewards of positive data that sustained me and allowed me to continue," she says. "I don't think my lack of confidence is unique, and it's important for young scientists to realize that," she says.

"You also need a life outside the lab, whatever that is, so that you have perspective and can face every day with a more positive attitude," Zoghbi explains. For her, life outside the lab has been her husband, son, daughter, and her extended family in Lebanon. She and William began to take their children on visits to Lebanon as youngsters, to experience the country's beaches, mountains, and culture, and they continue the tradition with their grown children and first grandchild. ■

Robb Rutledge: Happiness Hunter

Principal Research Associate, University College London, Age: 37

BY SHAWNA WILLIAMS

During an experiment in which people played a game and won or lost money, neuroscientist Robb Rutledge noticed something strange. "Some people would be in a really good mood, and it wouldn't actually be closely related to how much money they had," he says. "That seemed very surprising to me."

Rutledge, then a grad student studying the neuroscience of decision making at New York University, wondered whether it would be possible to figure out what determines those moods—specifically, how happy a person feels minute-to-minute. He went on to do a postdoc at University College London (UCL), where he ran similar experiments in which volunteers played a game for money, but this time he focused on constructing a model for what factors determined the players' emotional responses to outcomes. Rather than the amount of their winnings, what mattered most to players' moods was whether the reward exceeded their expectations.[1]

Based on previous work by other researchers, Rutledge suspected the neurotransmitter dopamine was involved in the moods study participants reported. So he and colleagues ran money-winning experiments on people who'd been given a drug that increases dopamine release. Compared with people given a placebo, people who got the drug reported feeling better after small wins. But there was no difference in how the two groups felt after larger wins or losses.[2] Dopamine, while important, isn't the whole story, Rutledge says. There must be other systems in the brain that inform how we feel after these types of events. He and his colleagues are now searching for those systems.

Even if he finds them, Rutledge doesn't think his findings are likely to improve happiness in healthy people. He's more interested in helping people with depression. A few years ago, he and colleagues did fMRI scans of people with depression and healthy controls as they performed a task with associated rewards. The team also built a smartphone app, The Great Brain Experiment, and had 1,833 volunteers rate their happiness levels as they played games and earned or lost points. People with depression and controls displayed similar patterns of brain activation and boosts in mood in response to unexpectedly large rewards, a finding that contrasts with previous results.[3]

Peter Dayan, a computational neuroscientist at UCL, says he was skeptical about the app in the beginning and thought it was unlikely to deliver interesting data. But Rutledge, who started his own lab at the university early last year, was able to construct experiments that surpassed Dayan's expectations. Dayan now thinks the use of The Great Brain Experiment, which has topped 134,760 users as of October 1, and other apps will turn out to be game changing because of the large quantity of data they can deliver to researchers.

"Robb has really pioneered the use of smartphone technology to do large-scale population studies of psychological processes and link those processes to mental health and mental illness," says Molly Crockett, a psychology researcher at Yale University. She did a postdoc at UCL at the same time as Rutledge and still collaborates with him to investigate how people form and change impressions of others. "Robb has really inspired the rest of the team in this research." ■

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Temperature as Tool

Thermogenetics brings neural circuits into focus.

BY DEVIKA G. BANSAL

Tools that use light, drugs, or temperature to make neurons fire or rest on command have become a mainstay in neuroscience. Thermogenetics, which enables neurons to respond to temperature shifts, first took off with fruit flies about a decade ago, but is emerging as a new trick to manipulate the neural functioning of other model organisms. That's due to some advantages it affords over optogenetics—the light-based technique that started it all.

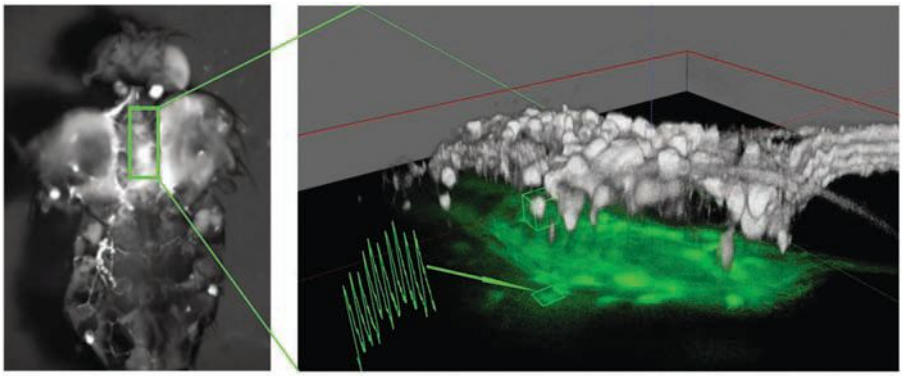
Genetic toolkits such as thermogenetics and optogenetics follow a basic recipe: scientists pick a receptor that responds to an external cue such as temperature or light, express the receptor in specific neurons as a switch that changes the cell's voltage—triggering or inhibiting firing—and then use the cue to turn the neural switch on or off.

Optogenetics revolutionized our understanding of how the brain's wiring affects animal behavior. But it comes with drawbacks. For one, delivering light into the deepest regions of the brains of nontransparent animals is a challenge. In mice, this requires surgically inserting optical fibers into the brain, tethering the animal to the light source. Researchers working with adult fruit flies can cut a window through the head cuticle to access the brain. In both cases, the necessary experimental setups are invasive and often time and effort intensive.

Additionally, the light intensity required for optogenetics tends to damage tissue. "You pump a lot of light through the optical fiber to activate neurons," says Vsevolod Belousov, a biochemist at the Russian Academy of Sciences in Moscow who develops thermogenetic tools. "In general, this is not avoidable."

Thermogenetics allows neuroscientists to sidestep these issues by harnessing proteins that respond to changes in temperature with stronger levels of activation than light-triggered switches, with less-invasive stimulus delivery. Unlike the light receptors of optogenetics, however, most of the thermoreceptors currently in use only allow researchers to turn neurons on, but not off; and their use in rodents is still evolving.

Here, *The Scientist* lays out the current state of the thermogenetic toolbox for different model organisms.



A TASTE OF TEMPERATURE: Adult *Drosophila* ventral nerve cord motor neurons expressing the gustatory thermoreceptor Gr28bD (left); in gray is a 3D reconstruction of the motor neurons, in green is neural activity in response to heat, with the green trace showing calcium currents in a single neuron (right).

TURNING THE HEAT ON FRUIT FLIES

Thermogenetics owes its humble beginnings to *Drosophila* research and is by far most developed for use in fruit flies. In the early 2000s, Toshihiro Kitamoto first used a mutated form of a protein called shibire to shut down synaptic communication in specific fly neurons at temperatures above 29° C. Shibire is an enzyme in the dynamin superfamily, which is involved in vesicle formation; its mutant version inhibits chemical transmission in a wide range of neurons within a few minutes of a temperature hike. But because dynamins affect many cellular processes, the use of shibire can have far-reaching, nonspecific effects.

Another class of proteins called thermoTRPs is more suitable for thermogenetics. ThermoTRPs are cation channels of the transient receptor potential family that normally mediates temperature preferences, both in the brain and elsewhere in the body. These channels respond dramatically to temperature shifts as small as 1°–2° C. The *Drosophila* TrpA1, for example, turns on slightly above 25° C, and the rat TRPM8 turns on just below 25° C.

When scientists first expressed TrpA1 in the motor neurons of fruit flies, they found that heating up the cells paralyzed the animals. "We got warm water and started dunking them in and that just made them pass out," says Paul Garrity, a biologist at Brandeis University who pioneered the use of thermoTRPs. "It was like a magic trick."

TRP channels also conduct ions very efficiently, says Belousov—at about 1,000-fold higher flux than the ion channels used in optogenetics. This means that thermoTRPs can drive robust activation at low expression levels, reducing toxic effects of overexpressing proteins.

Fruit fly researchers have yet another option: Gr28bD, a gustatory receptor that was recently found to respond to heat in

MISHRA ET AL., *SCI REP*, 8:901, 2018

fruit fly neurons, although at the much higher temperatures of 32° C to 36° C. Researchers at the University of Missouri in Columbia are developing the protein as another thermogenetic tool. So far, the Gr28bD receptor works when expressed in *Xenopus* oocytes and in motor neurons of adult fruit flies (*Sci Rep*, 8:901, 2018).

Like thermoTRPs, Gr28bD is a cation channel, which only allows researchers to activate neurons, says Mirela Milescu, a University of Missouri biophysicist studying the structure-function relationship of this protein. The hope, she says, is to engineer it to work at a lower activation temperature, and perhaps even to turn it into an inhibitory tool.

The thermoreceptor proteins shibire, thermoTRPs, and Gr28bD can all be activated by changing ambient temperature in a so-called hot box, a fly container with a temperature regulator. The process is simple and noninvasive. But ambient heating has several disadvantages. For starters, the temperature change is slower than direct heat delivery, says Belousov, and spatial resolution is lacking because you activate the entire animal. For example, using a hot box, all the cells with TrpA1 in *Drosophila* get activated and stay active for the duration of the experiment. "Until you cool down, those channels are open and the neurons remain depolarized," he says. "This is not how neurons normally behave; they fire in pulses."

To address that limitation, Barry Dickson, a neuroscientist at the Howard Hughes Medical Institute's Janelia Research Campus in Ashburn, Virginia, built a more targeted heat-delivery system. The Fly Mind Altering Device, or FlyMAD, uses a video camera to track a fly as it moves around in a box. Upon locating the fly, the device shines an unfocused infrared beam to deliver heat directly to its head, allowing researchers to target the brain and to activate thermogenetic proteins more quickly (*Nat Methods*, 11:756–62, 2014).

Overall, thermoTRPs can only be used to activate neurons because they bring cations into the cell. Belousov and others, however, are engineering these channels to switch conductance from calcium to chloride ions, which will allow them to inhibit neural activity as well.

GETTING THERMAL WITH ZEBRAFISH

Most zebrafish neuroscience studies are performed using embryos and larvae, because many of the advantages of juvenile zebrafish—small size, transparency, and a small and simple brain—are lost in adults, says David Prober, a neurogeneticist at the California Institute of Technology in Pasadena.

We wanted an alternative approach that didn't use a visual stimulus to activate the neurons.

—David Prober, Cal Tech

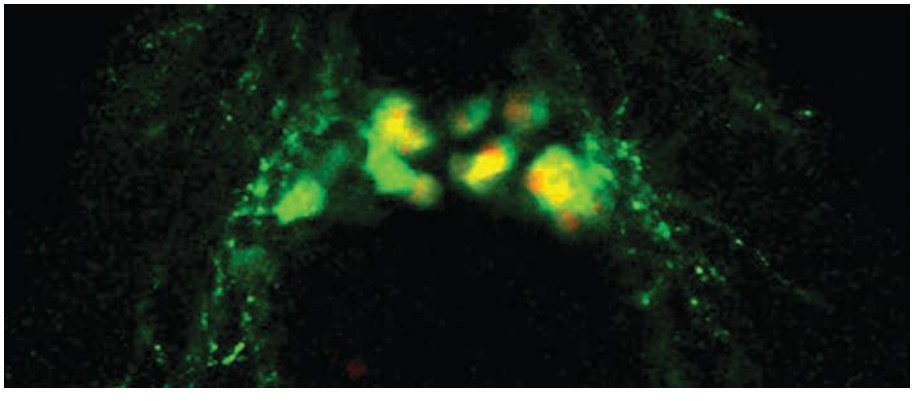
Larvae's transparency means researchers can use ambient lighting to access any neuron in the brain noninvasively with optogenetics. The problem, however, is that seeing the light turn on induces a behavioral response in the animals, says Prober. "So we wanted an alternative approach that didn't use a visual stimulus to activate the neurons."

Prober's lab tested another TRP channel called TRPV1, which gets activated close to 43° C as well as by capsaicin, the molecule that makes chili peppers hot. At a low concentration of capsaicin, TRPV1 activation causes neurons to fire; at a higher concentration, its over-activation causes those neurons to die. TRPV1 can thus switch neurons both on and off, although the off switch is permanent. Capsaicin-induced TRP channel activity lacks the millisecond control of optogenetics, but its effect over the course of seconds works for behaviors that occur over a long timescale, such as sleep (*Nat Methods*, 13:147–50, 2016).

Another receptor from the thermoTRP family that is showing promise in zebrafish research is rattlesnake TRPA1, which turns on around 28° C. That's well within zebrafish's physiological range, yet high enough so that larvae can be raised at ambient temperatures without activating the channel. In contrast, *Drosophila* TrpA1, which turns on slightly above 25° C, would be incompatible with use in zebrafish studies because 25° C is the lowest temperature at which scientists raise the animals, says Prober.

Like fly researchers, fish scientists also use ambient heating to activate neurons. However, Belusov's team recently developed a heat delivery system that can shine focused infrared radiation at single cells using a fiber optic rig.

"This can even be called a branch of optogenetics," says Belousov, because they still use light as an activating stimulus, except that it is not in the visual but in the



FEVER FISH: The hypothalamus of a five-day old zebrafish larva expresses green fluorescent protein and the thermoreceptor TRPV1 fused to a red fluorescent protein.

DAVID PROBER, CALTECH

invisible infrared range. His team tested the method by directing the infrared beam at embryos embedded in agarose. They are now developing ways of using this system in actively behaving zebrafish larvae (*Nat Comms*, 8:15362, 2017).

WARMING UP TO MAMMALS

Optogenetics is widely used in mammals, but its invasiveness and the low conductance of channelrhodopsins—the photoreceptive channel proteins that are modified for use in optogenetics studies—have led researchers to explore thermogenetics.

ThermoTRPs have a much higher conductance, turning on neurons with little external stimulation. But finding a thermoTRP that works at around 37°–38° C, the physiological temperature of mammals, has so far been challenging. Neither rat TRPM8, nor fly TRPA1 nor rattlesnake TRPA1 can be used in mammals because their activation thresholds are far below mammalian body temperatures.

TRPA1 from the rat snake, however, is active around 38.5° C, which is fairly close to mammalian brain temperature, says Belousov. His lab reported that this channel could activate cultured rodent neurons (*Nat Comms*, 8:15362, 2017), but its performance in behaving mice remains to be shown.

Ultimately, for all of the methods, the name of the game is trying to get a really short spike and then immediately turning off your stimulus.

—Polina Anikeeva, MIT

Scientists have also used rat TRPV1 to activate cultured mammalian cells. Even though the temperature at which half the TRPV1 channels are activated is thought to be around 42° C, Arnd Pralle, a biophysicist at the University at Buffalo, New York, successfully used TRPV1 at 39° C to activate neurons in the motor cortex, dorsal striatum, and in the ridge between dorsal and ventral striatum of freely moving mice. At that temperature, only about 15 percent to 20 percent of TRPV1 channels open, but the resulting calcium current is enough to turn on the neurons (*eLife*, 6:e27069, 2017).

"You're not trying to keep the temperature at 43° C for several minutes," says Polina Anikeeva, a neural nanotechnologist at MIT. "Ultimately, for all of the methods, the name of the game is trying to get a really short spike and then immediately turning off your stimulus."

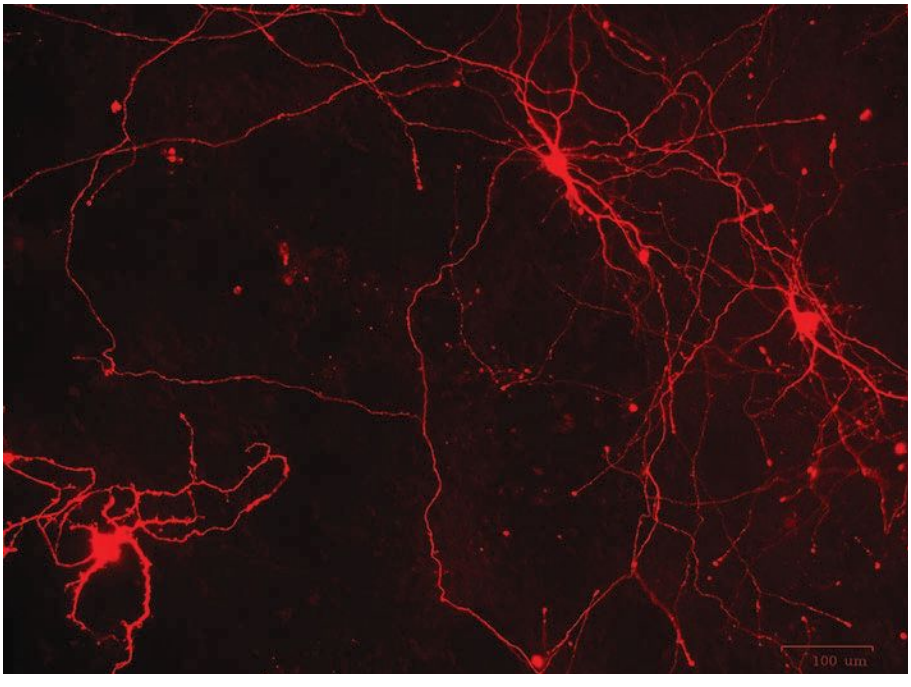
Unlike in fruit flies and zebrafish, of course, ambient warming doesn't raise the temperature of warm-blooded animals. The field desperately needs new ways to wirelessly deliver energy deep into the tissue, says Belousov. The focused infrared beam that his team developed works as a vehicle for thermal delivery at single-cell resolution until about 2–3 mm deep into the brain by adjusting wavelength and pulse duration. But stimulating areas deeper in the brain still requires the surgical implantation of fibers.

Although limited, infrared radiation is still absorbed by the body, curbing penetration depth, says Anikeeva. "The only field that our body truly does not couple to is magnetic."

Pralle, Anikeeva, and others are therefore developing "magnetothermal" approaches, in which magnetic nanoparticles are injected into the brain and activated by a high-intensity magnetic field. The neuro-localized magnets then convert that localized magnetic energy into heat, which in turn activates TRPV1 channels. Using this technique, Pralle's team was able to tweak the brain regions responsible for walking, rotational, and freezing behavior in untethered mice (*eLife*, 6:e27069, 2017).

Recently, Pralle's team demonstrated the use of a thermosensitive chloride channel, anoctamin 1 (TMEM16A), to silence neurons in rat hippocampal cultures using magnetic nanoparticles. The channel's big benefit is that upon activation, around 38°–39° C, it inhibits neurons (*Front Neurosci*, 12:560, 2018).

"The end goal is really to use all these techniques to turn different regions of the brain on and off and analyze the circuits that play together," says Pralle. ■



RED HEAT: These mouse primary embryonic neurons glow red because they are expressing the rat snake thermoreceptor TRPA1 tagged with a red fluorescent protein.

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Looking Inward

Student organizations have long recognized the need for mental health support during graduate school. Now, university staff are getting involved too.

BY ABBY OLENA

In 2013, when Wendy Ingram was a fourth-year graduate student in the department of molecular and cell biology at the University of California, Berkeley, a classmate became severely depressed, took a leave of absence from the program, and eventually committed suicide. Ingram and her friends were more than shocked. "We were devastated, and we were frustrated," says Ingram, now a postdoc at Johns Hopkins University. "We saw gaps in care and gaps in knowledge and gaps in understanding of what would have been helpful things to do."

Spurred by that heartbreaking loss, Ingram and eight classmates in UC Berkeley's Molecular Cell Biology (MCB) program created the MCB Graduate Network. The graduate student–led group organizes students-only discussions targeted to each year of graduate training, where seasoned students talk with less-advanced colleagues about navigating the big milestones of that year, such as picking a lab or taking a qualifying exam. The program's organizers also facilitate a mentorship program, in which new students meet with two upper-year students at least once a month during the fall of their first year. Plus, the group maintains a website that includes a list of resources available to MCB students in a variety of areas: mental health, physical health, personal and legal support, career development, and financial concerns.

Like many organizations promoting graduate students' mental health around the US, the MCB Graduate Network is run by and for students with support, but minimal involvement, from faculty and staff. But there are calls to expand the institutional footprint in this arena. Anecdotal evidence from mental health practitioners and students, and, more recently, research findings, reveal that depression and anxiety are unusually prevalent among graduate students. And momentum is gathering among institutional administrators and principal investigators to respond by offering better and more-appropriate support to their trainees.

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"There always will be mental health concerns" for graduate students, Brianne Howard, the director of academic support at the University of British Columbia (UBC), tells *The Scientist*. But institutions can help, she says, by combining a proactive approach—that is, finding out what the stressors are and trying to mitigate them—with efforts to make sure that faculty and staff are ready to act when students are really struggling.

A widespread phenomenon

In 2017, Frederik Anseel, a psychologist at King's College London, and colleagues compared mental health data from more than 3,500 PhD students in Belgium to those of people in the same age group with similar educational backgrounds who were not in graduate school. They found that half the PhD students had experienced recent psychological distress, and a third were at risk for developing a psychiatric disorder such as depression. There were twice as many mental health problems among the PhD students as in the control group.

That difference surprised Anseel. He explains that, starting grad school, PhD

students in Belgium tend to make a bit more money than their counterparts who choose to work outside academia, and that, typically, highly educated individuals have lower instances of mental health problems. "Normally, you would expect the opposite pattern because these [students] are very highly educated people earning a good salary," he says.

But such findings are no surprise to Maggie Gartner, a psychologist who retired in January from her role as executive director of student counseling services at Texas A&M University. She has worked in counseling centers since 1984—often with graduate students, both individually and in groups. Gartner explains that one of the big issues graduate students face—and one she has seen throughout her career—is the expectation to excel in a variety of roles. "They are pulled 20 ways from Sunday," she says. "They try to do their best in one area, and that means it's not as good in another area because they just can't give it enough time."

As Anseel and his team looked into the factors associated with mental health status in the student population, they identified multiple areas of concern. Although the observational study could not determine causative factors, researchers found that worries about the competitive academic job market, poor career prospects, lack of control, inadequate support from colleagues, work-life imbalance, and a difficult supervisor-student relationship were all linked to psychological distress.

That last factor can be particularly difficult, says David Sacks, a psychologist with a private practice in Nashville, Tennessee, who has frequently seen problems arise in this area during his work with graduate students. Until June, he also counseled students and postdocs in biomedical research at Vanderbilt University. When a conflict arises between a mentor and a trainee, whoever is called in to mediate tends to defer to the faculty member because they have more power, he says, meaning students' needs often go unaddressed and patterns of mistreatment are likely to continue.

Combined, all the sources of graduate school stress build up into emotional adversity that can affect student performance, Sacks adds. "Very rarely do people fail due to not being intellectually gifted enough to do the work," he says. "It's coping with rejection. It's balancing the things you have to give up and sacrifice. It's focusing too much on the outcome rather than the process because the reward is so far off in the future."

Since Anseel published his results in the May 2017 issue of *Research Policy*, students from around the world have reached out to him to comment on the similarity of their experiences to those described in the paper, suggesting the findings apply far beyond the study population. But other groups' research also indicates that some segments of the graduate student community are much more likely to experience mental health problems than others.

For a 2018 study, a group of researchers from around the US recruited more than 2,200 graduate students through social media and email to take a survey that included clinical scales for both anxiety and depression. Of the respondents, 41 percent reported scores indicating anxiety and 39 percent scored as depressed. Female trainees were more likely to be depressed and anxious than their male colleagues, while transgender and gender-nonconforming participants had the highest rates of anxiety and depression.

The study helps "showcase the support that is needed for [female and transgender graduate students] in academia," says study coauthor Teresa Evans, an assistant professor of pharmacology at the University of Texas Health Science Center in San Antonio. She adds that the 2018 study only skims the surface of the mental health differences among groups of graduate students, an area that needs more research, especially into the root causes. A recent consensus study report from the National Academies of Science, Engineering, and Medicine points to the role of sexual and gender harassment, which disproportionately affects women and transgender individuals, and also calls for more research.

Towards support

As evidence of mental health problems in graduate students piles up, several institutions have begun complementing the work of student organizations by making changes that are designed to improve the school environment.

> It's a professional duty to recognize stress and mental health among people we supervise.
>
> —Phil Buhlmann, University of Minnesota

One of the researchers spearheading such efforts is chemist Phil Buhlmann of the University of Minnesota Twin Cities. When he started as the director of graduate studies in his department six years ago, he made it his mission to support graduate student mental health department-wide—a move that was strongly supported by his colleagues. "It's a professional duty to recognize stress and mental health among people we supervise," Buhlmann says. What's more, faculty "really care about their graduate students. They take pride in graduate students who do well, so they want to help." Students and faculty can consult with Buhlmann, who now serves as a mental health advocate, when they have a concern, and he typically directs them to the right resources on campus.

Graduate students in the chemistry department also collaborated with Buhlmann and the university's health services to develop a survey, which they conduct every two years to assess graduate students' mental, social, and physical health. Buhlmann and the students recently published a study describing this project in the *Journal of Chemical Education*, in the hopes of helping other students and faculty who want to improve graduate student well-being.

Administrators are making similar efforts at other institutions. In the past five years, universities around the US have announced task forces—generally composed of administrators, faculty, staff, and students—to monitor and make recommendations about undergraduate and graduate student mental health.

In 2016, one such task force, at Johns Hopkins University in Baltimore, conducted listening sessions and a mental health survey of more than 2,300 students. The following year, the group issued draft recommendations, soliciting feedback from university students, faculty, and staff; last February, they released a final report. Task force cochair Daniele Fallin of the Johns Hopkins Bloomberg School of Public Health says that such reports help identify barriers to improving mental health. At Hopkins, "it was very clear that we needed better awareness of what's available, so that people can be better coaches and advisors to their own graduate students," she says.

UBC's Howard, meanwhile, along with Susan Porter, the dean and vice provost of graduate and postdoctoral studies, is working with the university's counseling services to address the immediate mental health needs of graduate students. They are currently testing two programs: one to help departments identify and alter parts of the training process that tend to present mental health challenges to students, and another to provide counseling specifically for grad students. Porter and Howard have also worked to offer mental health support at atypical locations—the university library or hospital, for instance—so that graduate student teaching assistants can avoid uncomfortable encounters with their students at the normal counseling service sites. Off campus, grad students have access to 24/7 counseling services via phone or video chat that they can use when they're doing fieldwork or learning a technique in a lab abroad.

Despite these initiatives, university involvement in graduate student mental health varies widely, and there is little in the way of a unified effort to address the issues across the academic spectrum. According to a survey of graduate deans conducted by the Council of Graduate Schools (CGS), an organization of about 500 institutions in the US and Canada, many administrators have concerns that their universities are not doing enough and that faculty might not be as prepared as other staff to direct students in crisis to appropriate resources. Porter and others, meanwhile, emphasize the ongoing need for long-term cultural change to improve the mental health environment in grad schools.

Nonetheless, interest in possible solutions is building, says Hironao Okahana, who led the survey and is the CGS associate vice president of research and policy analysis. The council has convened two meetings with sessions on graduate student mental health within the last year to facilitate connections among people working with students, and organizers are planning another such session for the council's annual meeting in December.

The University of Kentucky's Nathan Vanderford, a coauthor of the 2018 study, says that funding organizations, such as the National Science Foundation, could also make a difference by requiring attention to graduate student mental health, in the same way they've made training in responsible research conduct mandatory for recipients of training grants. "There needs to be a bigger push to make [graduate student mental health] a priority," he says, "because institutions are going to continue doing what they're doing unless they're motivated to do something else." ■

Abby Olena is a freelance science journalist based in Carrboro, North Carolina.

HOW YOU CAN SUPPORT GRAD STUDENTS

Check in: If you suspect someone is struggling with a mental health issue, don't stay silent, says Emily O'Hara, a licensed independent clinical social worker at the University of Minnesota Twin Cities. "We get asked the question all the time from faculty and staff, 'What if I say something, and it makes it worse?' [But] if you see something, say something, and worry less about saying the right thing."

Listen: According to Maggie Gartner, former executive director of student counseling services at Texas A&M University, the most supportive faculty "listen to their graduate students. They give them time, and that's a precious gift because faculty don't have that much time either."

Destigmatize help-seeking: David Sacks, a psychologist in Nashville, Tennessee, compares graduate mental health support to that provided by a sports coach. "No one talks about the stigma of getting a coach to help with your strength and conditioning. It doesn't mean you're admitting you're physically weak when you hire a personal trainer," he says. "We figure this is something you do if you want to maximize your potential."

Monitor mental health in your program: "You need to have a monitoring system because often otherwise you just have anecdotes and isolated events, and you have no idea how stressful the environment is," Frederik Anseel, a psychologist at Kings College London, tells *The Scientist.*

Consult the experts: Mental health professionals are eager and willing to speak with faculty or staff members who have concerns about a student, says Gartner. "I don't know a counseling center director who does not encourage consulting." She tells faculty and staff, "Yes, you should call me. We will help you deal with the situation."

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Science and Sensibility

In a new book, a vaccine researcher describes the scientific facts and personal anecdotes behind his family's experience with autism and its comorbid disabilities.

BY PETER HOTEZ

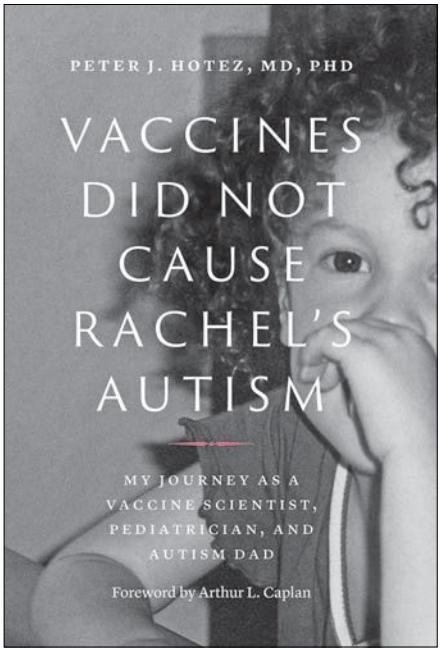
So far, the year 2018 has been a good news/bad news story with regard to vaccinating the world's children. On the positive side, Gavi, The Vaccine Alliance, recently announced that it's on track to immunize 300 million children in developing nations within Africa, Asia, and Latin America by the year 2020. But in Europe and the United States we've seen a slip in vaccine programs. The World Health Organization just announced that Europe experienced more than 40,000 measles cases during the first half of 2018—largely attributed to a lack of immunization—while in the US my collaborators and I identified communities in some states where large numbers of schoolchildren are not being vaccinated. The situation in both Europe and the US exists mostly because of well-organized antivaccine movements alleging that vaccines cause autism.

I wrote *Vaccines Did Not Cause Rachel's Autism* in response to the rapid acceleration in vaccine exemptions across the US and especially in Texas, where I develop neglected-tropical-disease vaccines as a pediatrician-researcher working at Baylor College of Medicine and Texas Children's Hospital. My book explains in depth why vaccines do not cause autism, based on the epidemiologic evidence refuting any links between autism and vaccines and also on the science of the developmental neurobiology of autism and how it begins prenatally. In parallel, I tell a deeply personal story about being a dad to Rachel, my 26-year-old daughter with both autism and significant intellectual disabilities, and her struggles living and working in our Montrose neighborhood of Houston.

Like many people on the autism spectrum, Rachel was first diagnosed as a child. At the time of her diagnosis I was a new assistant professor at Yale University setting up my vaccine research laboratory, while my wife Ann (and sometimes I) took Rachel to psychiatric visits at the world-famous Yale Child Study Center. The book relays some difficult periods, first in Connecticut and then in Maryland and Texas, as we tried to understand Rachel's behavior and come to grips with her significant disabilities. But it also contains moments of humor and joy, both from Rachel and the people who gravitated towards her.

In 1998, when Rachel was six years old, *The Lancet* published the now infamous, and ultimately retracted, paper asserting that the MMR vaccine was linked to pervasive developmental disorder, or what we now refer to as autism spectrum disorder. The paper launched a 20-year antivaccine movement that severely jeopardizes public health in the US and Europe. Antivaccine activities are on the verge of becoming global and reversing many of the public health gains that began with the launch of the UN's Millennium Development Goals.

I wrote *Vaccines* in the hope that it will educate vaccine-hesitant parents and support pediatricians, nurses, and other health professionals who are faced with the prospect of defending vaccines on a daily basis. *Vaccines* provides tools for both parents and health professionals dealing with an aggressive and well-organized antivaccine lobby. At the same time, the book offers a glimpse into the world of autism and autism parenting by portraying an honest and forthright story of one girl, her siblings, and her mom and dad. By alternating the science with our family's story, I hope the book provides a unique, compassionate, and visceral understanding of both vaccines and autism, and also autism's associated comorbidities. ■



Johns Hopkins University Press, October 2018

Peter Hotez is the dean of the National School of Tropical Medicine at Baylor College of Medicine in Houston and the director of the Texas Children's Hospital Center for Vaccine Development. Read an excerpt of Vaccines Did Not Cause Rachel's Autism *at www.the-scientist.com.*

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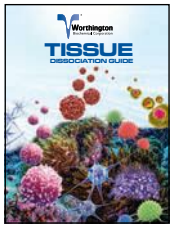

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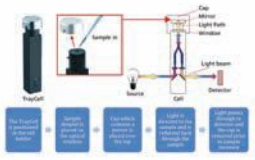

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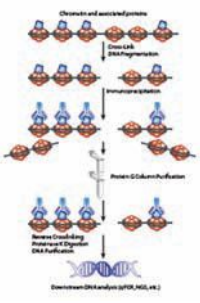

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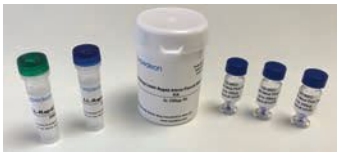

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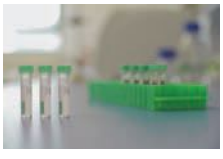

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Cranial Craters, 1000-1250

BY SUKANYA CHARUCHANDRA

In the long history of trepanation—removing a piece of the human skull—residents of the Andes were relative latecomers, likely beginning the practice around 400 BCE, based on archaeological data. But ancient Peru stands out for the variety of techniques used and the scale at which trepanation took place. More than 800 pre-Columbian trepanned skulls have been discovered in that country, more than in any other place in the world.

Many of those were unearthed by a team led by Danielle Kurin, a bioarchaeologist at the University of California, Santa Barbara. Beginning in 2010, she and her colleagues excavated several burial caves containing the skeletal remains of 284 Chankas, a people known to have been mortal enemies of the Incas. Of those, 32 had holes in their skulls—sometimes more than one. The holes "were clearly man-made," says Kurin. "They had some kinds of cut marks." Based on marks on the skulls, and on archaeological and anthropological evidence from millennia of Andean culture, she thinks the Chankas used trepanation to treat inflammation of the brain, head injuries, and as a portal to welcome a frightened soul back into its body.

The Chankas made the holes by scraping away at the skull bone, boring or drilling holes into it, or by cutting in circles or lines. Their tools included obsidian knives and other sharp stones. Among the archaeological remains, which dated back to circa 1000-1250 CE, Kurin also found drill bits that matched the sizes of the trepanned holes. This suggests, she says, that the Chankas had a "standardized toolkit."

Many patients survived the procedure: Kurin found bony extensions around the edges of their skull holes, evidence of healing. Other mummified skulls with closely shaved hair around the holes show signs that people had applied a poultice to the wound site. "What we think we're seeing over time is them kind of experimenting with different surgical techniques," says Kurin. Patients whose holes were formed from scraping were the most likely to survive, followed by those whose skulls had been cut into; subjects whose skulls were drilled into were the least likely to recover. Kurin also found that practitioners had trepanned dried, long-dead skulls in various ways, perhaps indicating that they were refining the techniques for use on the living.

Trepanation in Peru ended with the Spanish conquest.

Archaeologist and newspaper editor Ephraim George Squier, sent to the country by Abraham Lincoln in 1863, acquired the first-known trepanned skull from a cemetery near Cuzco, Peru. The members of the New York Academy of Medicine examined the cuts around the rectangular hole in the skull and determined that it was made by human hands.

From about 1000-1400 CE, residents of what's now Peru had a success rate almost twice as high as that of Civil War battlefield doctors of Lincoln's time who performed trepanations to treat head wounds. Though the ancient Andeans lacked knowledge of microbes or anesthesia, they weren't operating in germ-ridden hospitals, and they used newly made instruments for each patient, notes Kurin.

She points out that the time period of the skulls she found was one of cultural turmoil for the Chankas, following the collapse of the Wari Empire, the political system that had ruled them for about 500 years. "Along with this deprivation and violence, we see innovation and resilience," she says. "We're seeing people who are not giving up . . . they're innovating, and developing over time a pretty intense and invasive therapeutic means of saving lives. And in many cases, they're successful and [the patients are] being cared for by the community." ■

DANIELLE KURIN

HOLES IN THE HEAD: The skull of a young Chanka man who lived between 1170-1270 shows evidence of two trepanations performed years apart. Kurin notes that the hole near the top of the head was made first, likely with a hand drill, while the hole above the eye was made through repeated scraping with a sharp stone.

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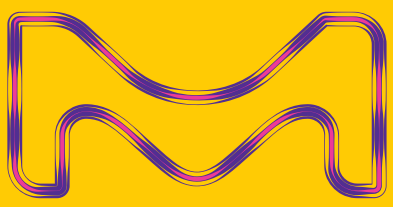

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