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THE GUT-BRAIN CONNECTION

Appetite, metabolism and weight are regulated by a complex neuro-network

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Secrets to Building a Super-Memory • Decoding Babies' Cries • Can Pills Stop Suicide?

SPENCER HEYFRON

FROM THE EDITOR

Welcome to the New *Scientific American Mind*

One of the many wondrous things about our minds is how adaptable they are, shifting with our experiences and in response to the environment around us. Now *Scientific American Mind,* initially begun in 2004 as a print edition that was reproduced in PDF archives, has fully undergone a digital transformation. Oh, you can still turn the pages on your tablet or mobile phone, but they will no longer be made of ink and paper.

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The new *Scientific American Mind* will still bring you insightful, sprightly stories from both researchers who are experts in their fields and award-winning science journalists. In this edition, for instance, Sue Johnson, a clinical psychologist and professor emeritus at the University of Ottawa, explains how couples can stay attached in "Deciphering the Language of Love." Learn how gut bacteria rule our appetites in a special report, including "How Gut Bacteria Tell Their Hosts What to Eat," by Knvul Sheikh, and "Mind over Meal: Does Weight-Loss Surgery Rewire Gut-Brain Connections?" by Bret Stetka. There's much more in this issue to explore as well.

As we hope you'll agree, *Scientific American Mind* remains the essential guide to a lifetime's journey to understand our innermost selves. We'd love to hear what you think, please email your feedback to sadigital@sciam.com.

Mariette DiChristina
Editor in Chief

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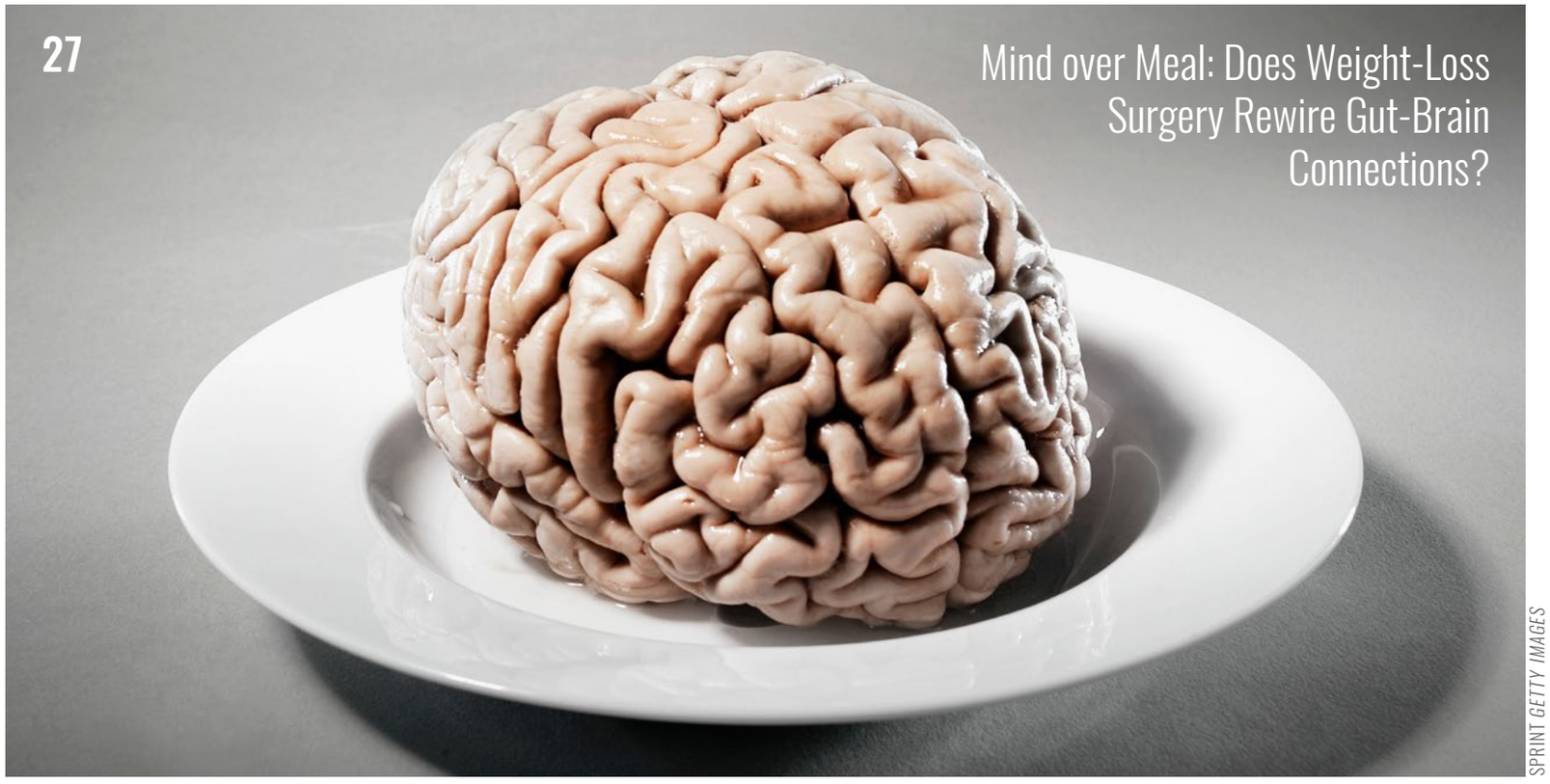

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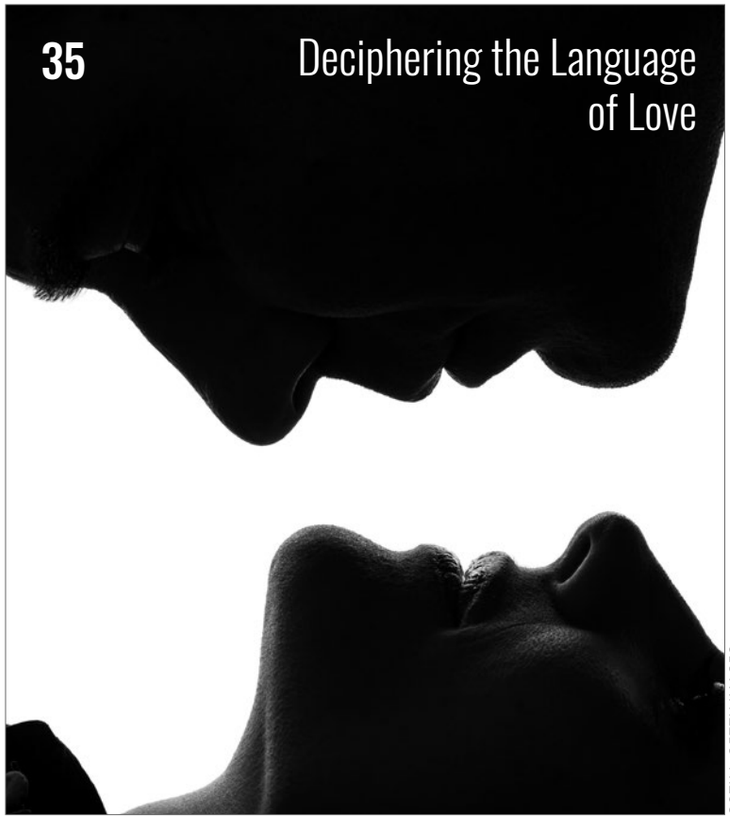

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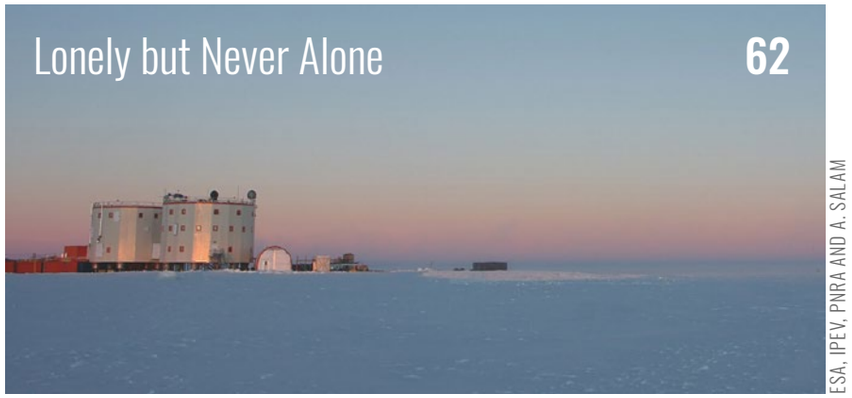

ESA, IPEV, PNRA AND A. SALAM

Colored scanning electron micrograph (SEM) of *Lactobacillus* bacteria.

STEVEN GSCHMEISSNER *GETTY IMAGES*

NEWS

How Gut Bacteria Tell Their Hosts What to Eat

By suppressing or increasing cravings, microbes help the brain decide what foods the body “needs”

Scientists have known for decades that what we eat can change the balance of microbes in our digestive tracts. Choosing between a BLT sandwich or a yogurt parfait for lunch can increase the populations of some types of bacteria and diminish others—and as their relative numbers change, they secrete different substances, activate different genes and absorb different nutrients.

And those food choices are probably a two-way street. Gut microbes have also been shown to influence diet and behavior as well as anxiety, depression, hypertension and a variety of other conditions. But exactly how these trillions of tiny guests—collectively called the microbiome—influence our decisions on which foods to stuff into our mouths has been a mystery.

Now neuroscientists have found that specific types of gut flora help a host animal detect which nutrients are missing in food and then finely titrate how much of those nutrients the host really needs to eat. "What the bacteria do for appetite is kind of like optimizing how long a car can run without needing to add more petrol to the tank," says senior author Carlos Ribeiro, who studies the eating behaviors of *Drosophila melanogaster,* a type of fruit fly, at Champalimaud Center for the Unknown in Lisbon.

In a paper published recently in *PLOS Biology,* Ribeiro and his team demonstrated how the microbiome influences drosophila's nutritional decisions. First, they fed one group of flies a sucrose solution containing all the necessary amino acids. Another group got a mix that had some of the amino acids needed to make protein but lacked essential amino acids that the host cannot synthesize by itself. For a third group of flies, the scientists removed essential amino acids from the food one by one to determine which was being detected by the microbiome.

After 72 hours on the various diets, flies in the all three groups were presented with a buffet offering their usual sugary solution alongside protein-rich yeast. The researchers found that flies in the two groups whose diet lacked any single essential amino acid got a strong craving for yeast to make up for the missing nutrients. But when scientists increased five different types of bacteria found in the flies' digestive tracts—*Lactobacillus plantarum, L. brevis, Acetobacter pomorum, Commensalibacter intestini* and *Enterococcus faecalis*—the flies completely lost the urge to eat more protein.

The researchers found that the flies' amino acid levels were still low, indicating the bacteria were not simply replacing nutrients missing from the flies' diet by producing the amino acids themselves. Instead the microbes were functioning as little metabolic factories, transforming the food they got into new chemicals: metabolites that the researchers believe might be telling the host animal it could carry on without the amino acids. As a result of this microbial trick, the flies were able to continue reproducing, for example—even though an amino acid deficiency usually hampers cell growth and regeneration and therefore reproduction, Ribeiro explains.

Two kinds of bacteria were particularly effective in influencing the appetites of flies this way: *Acetobacter* and *Lactobacillus*. Increasing both was enough to suppress the flies' protein cravings and increase their appetite for sugar. These two bacteria also restored the flies' reproductive abilities, indicating their bodies were carrying out normal functions that typically get restricted when there is a nutritional deficiency. "How the brain handles this

trade-off of nutritional information is very fascinating, and our study shows that the microbiome plays a key role in telling the animal what to do," Ribeiro says.

Next the team removed an enzyme needed to process the amino acid tyrosine in flies, making it necessary for the flies to get tyrosine via their food, just like other essential amino acids. Surprisingly, they found that *Acetobacter* and *Lactobacillus* were unable to suppress the craving for tyrosine in the modified flies. "This shows that the gut microbiome has evolved to titrate only the normal essential amino acid intake," Ribeiro explains.

The research adds a new perspective on coevolution of microbes and their hosts. "The findings show there is a unique pathway that has coevolved between animals and the resident bacteria in their gut, and there is a bottom-up communication about diet," says Jane Foster, who is a neuroscientist at McMaster University in Ontario and not associated with the study.

Although the research does not specify the exact mechanism of communication, Ribeiro thinks it could take different forms. Strong evidence from the study indicates that microbially derived metabolites carry information from the gut to the brain, telling the host whether it needs a particular kind of food. "One of the big evolutionary mysteries is why we lost the ability to produce essential amino acids," he says. "Maybe these metabolites gave animals more leeway to be independent of these nutrients and to deal without them sometimes."

Microbes may have their own evolutionary reasons for communicating with the brain, he adds. For one thing, they feed on whatever the host animal eats. For another, they need host animals to be social so the guests can spread through the population. The data are limited to animal models so far, but Ribeiro believes that gut-brain communication can provide fertile ground for developing treatments for humans in the future. "It's an interesting therapeutic window that could be utilized to improve behaviors related to diet one day," he says.

—Knvul Sheikh

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GARY JOHN NORMAN *GETTY IMAGES*

NEWS

Cross-Cultural Evidence for the Genetics of Homosexuality

Mexico's third gender sheds light on the biological correlates of sexual orientation

The reasons behind why people are gay, straight or bisexual have long been a source of public fascination. Indeed, research on the topic of sexual orientation offers a powerful window into understanding human sexuality. The *Archives of Sexual Behavior* recently published a special section devoted to research in this area, entitled "The Puzzle of Sexual Orientation." One study, conducted by scientists at the University of Lethbridge in Alberta, offers compelling, cross-cultural evidence that common genetic factors underlie same-sex, sexual preference in men.

Among the indigenous Zapotec people in southern Mexico, individuals who are biologically male and sexually attracted to men are known as *muxes*. They are recognized as a third gender: *Muxe nguiiu* tend to be masculine in their appearance and behavior; *muxe gunaa* are feminine. In Western cultures, they would be considered gay men and transgender women, respectively.

Several correlates of male androphilia—sexual attraction of biological males to men—have been shown across different cultures, which is suggestive of a common biological foundation among them. For example, the fraternal birth order effect—the phenomenon whereby male androphilia is predicted by having a higher number of biological older brothers—is evident in both Western and Samoan cultures.

Interestingly, in Western society, homosexual men, compared with heterosexual men, tend to recall higher levels of separation anxiety—the distress resulting from being separated from major attachment figures, such as one's primary caregiver or close family members. Research in Samoa has similarly demonstrated that third-gender *fa'afafine*—individuals who are feminine in appearance, biologically male and attracted to men—also recall greater childhood separation anxiety when compared with heterosexual Samoan men. Thus, if a similar pattern regarding separation anxiety were to be found in a third, disparate culture—in the case of the state of Oaxaca in Mexico—it would add to the evidence that male androphilia has biological underpinnings.

The recent study included 141 heterosexual women, 135 heterosexual men, and 178 *muxes* (61 *muxe nguiiu* and 117 *muxe gunaa*). Study participants were interviewed using a questionnaire that asked about separation anxiety—more specifically, the distress and worry they experienced as a child in relation to being separated from a parental figure. Participants rated how true each question was for them when they were between the ages of six and 12.

Muxes showed elevated rates of childhood separation anxiety when compared with heterosexual men, similar to what has been seen in gay men in Canada and *fa'afafine* in Samoa. There were also no differences in anxiety scores between women and *muxe nguiiu* or *muxe gunaa*, or between the two types of *muxes*.

When we consider possible explanations for these results, social mechanisms are unlikely because previous research has shown that anxiety is heritable and parenting tends to be in response to children's traits and behaviors, as opposed to the other way around. Biological mechanisms, however, offer a more compelling account. For instance, exposure to female-typical levels of sex steroid hormones in the prenatal environment are thought to "feminize" regions of the male brain that are related to sexual orientation, thereby influencing attachment and anxiety.

On top of these observations, studies in molecular genetics have shown that Xq28,

a region located at the tip of the X chromosome, is involved in both the expression of anxiety and male androphilia. This work suggests that common genetic factors may underlie the expression of both. Twin studies additionally point to genetic explanations as the underlying force for same-sex partner preference in men and neuroticism, a personality trait that is comparable to anxiety.

The research points to childhood separation anxiety as a culturally universal correlate of androphilia in men. This has important implications for our understanding of children's mental health conditions because subclinical levels of separation anxiety, when intertwined with male androphilia, may represent a typical part of the developmental life course.

As it stands, sexual orientation research will continue to evoke widespread interest and controversy for the foreseeable future because it has the potential to be used—for better or worse—to uphold particular sociopolitical agendas. The moral acceptability of homosexuality has often hinged on the idea that same-sex desires are innate and immutable and therefore not a choice. This is clear when we think about how previous beliefs around homosexuality being learned were once used to justify now discredited attempts to change these desires.

The cross-cultural similarities evinced by the Lethbridge study offer further evidence that being gay is genetic, which is, in itself, an interesting finding. But we as a society should challenge the notion that sexual preferences must be nonvolitional to be socially acceptable or safe from scrutiny. The etiology of homosexuality, biological or otherwise, should have no bearing on gay individuals' right to equality.

—Debra W. Soh

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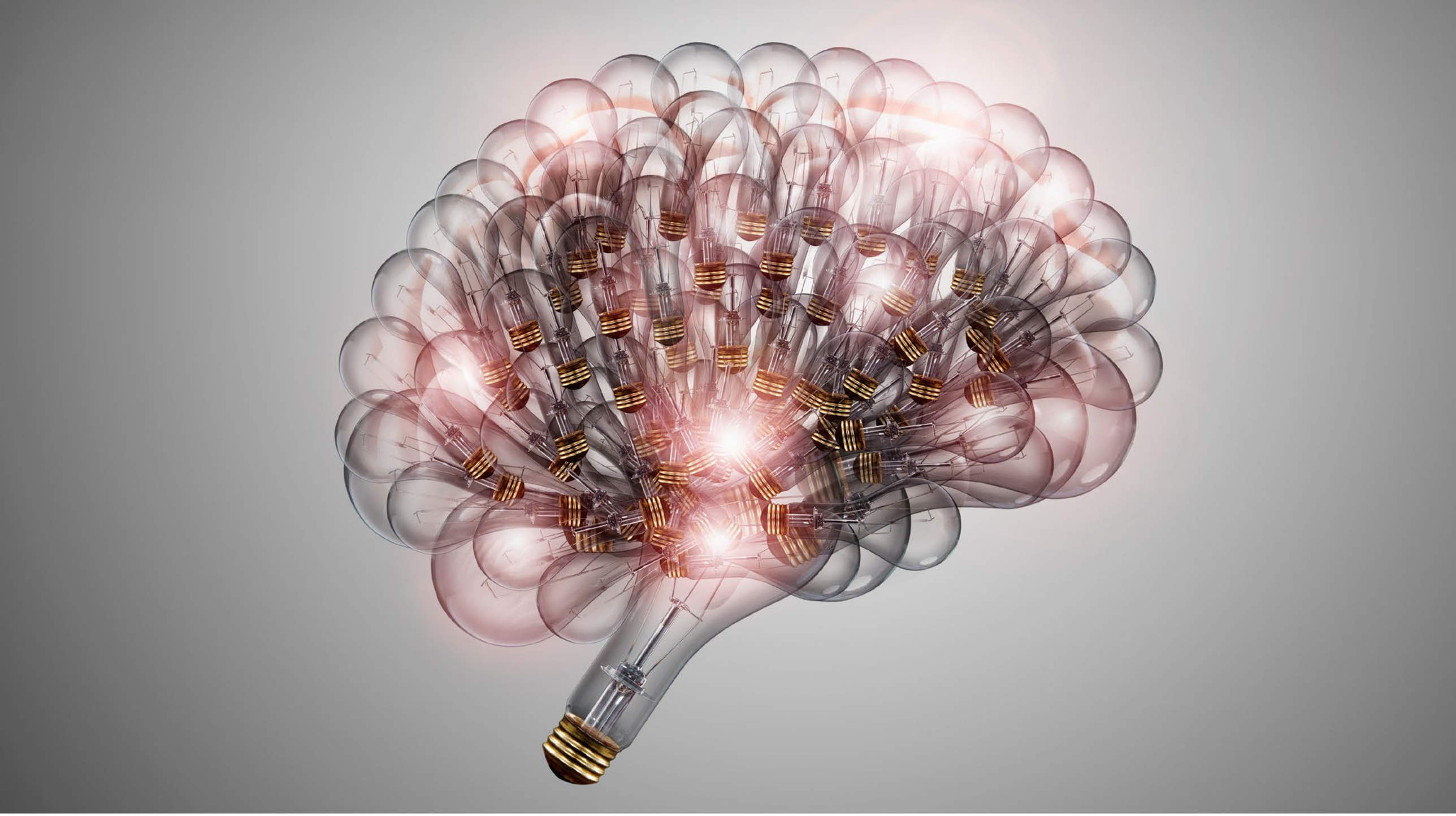

JOHN LUND *GETTY IMAGES*

NEWS

Don't Forget: You, Too, Can Acquire a Super Memory

Learning a memorization technique used by elite memory athletes leads to widespread changes in brain wiring

Elite memory athletes are not so different from their peers in any other sport: They face off in intense competitions where they execute seemingly superhuman feats such as memorizing a string of 500 digits in five minutes. Most memory athletes credit their success to hours of memorization-technique practice. One lingering question, though, is whether memory champs succeed by practice alone or are somehow gifted. Recent research suggests there may be hope for the rest of us. A study published in *Neuron* provides solid evidence that most people can successfully learn and apply the memorization techniques used by memory champions while triggering large-scale brain changes in the process.

A team led by Martin Dresler of Radboud University in the Netherlands used a combination of behavioral tests and brain scans to compare memory champions with the general population. It found that top memory athletes had a different pattern of brain connectivity than controls did but also that subjects who learned a common technique over a period of weeks, not years, greatly improved their memory skills and began to exhibit brain-connection patterns resembling those of elite memorizers.

Many of us learn new skills throughout our lives, and scientists have long wondered if, and how, our brain changes as a result. Previous research has linked some skills to specific changes. One well-known set of studies showed that London taxi drivers developed more gray matter in their hippocampus (a brain area linked to memory) as they acquired the knowledge needed to navigate the city's haphazard maze of streets. Dresler and his colleagues, motivated in part by co-author and professional memory trainer Boris Konrad, decided to focus on elite memory athletes who utilize techniques to compete at highly specific tasks such as memorizing decks of cards or lines of binary digits in minutes. They wanted to know whether these highly skilled practitioners exhibit noticeable brain changes and how those changes occur.

In the first part of the study the researchers matched 23 elite memory champions with control subjects based on age, gender and IQ. Both groups underwent a series of brain scans, including anatomical scans and functional MRI during a resting state—one in which subjects were not doing anything—and during a memory task. The researchers found the memory champions did not differ from the controls in any particular brain region but rather had different patterns of brain connectivity during resting-state and task-based fMRI scans. To Dresler, these results suggested "there's not a sort of general hardware difference in memory champions that allows them to reach these memory levels but that something subtler is going on," which spurred the team to investigate further.

Next, the researchers took 51 subjects who had never previously engaged in memory training and divided them into an experimental group and two control groups. Experimental subjects underwent six weeks of intense memory training for half an hour each day using the centuries-old method of loci strategy still popular with memory champions: They learned how to map new information such as numbers or names onto familiar spatial locations such as those in their homes. The active control group trained for a working memory task called the *n*-back that does not train long-term memory. Meanwhile the passive control group received no training.

After training, the experimental subjects improved significantly at memory tasks (whereas neither control group im-

proved) yet did not exhibit any structural brain changes. Their brain-connection patterns during resting-state and task-based fMRI scans, however, became more similar to those of memory champs, a change that correlated positively with memory improvements. "I think the interesting part is that not only can you boost memory in a similar way behaviorally in normal subjects compared with memory athletes," Dresler says, "but on the brain level you see a reflection of that behavioral increase, and you drive the brains of naive subjects into the patterns of the best memorizers in the world."

James McGaugh, a neurobiologist at the University of California, Irvine, who was not involved in the study, considers it to be in a similar vein as the research on London taxi cabs but highlights an important difference: rather than pinpointing a particular brain region, the study found an overall change in brain connections. "All our brains are malleable all the time, and this is just another piece of evidence of that," he says. "If you learn something, and you learn it well, the brain changes." For his U.C. Irvine colleague, Craig Stark, a professor of neurobiology and behavior who also was not part the research, it represents "a really interesting contribution to the field." Stark was particularly impressed by the study's clever experimental design, which he expects to be adopted by researchers in other domains. He adds that the results align with the idea that our brain is highly plastic and continuously changes and adapts. "This is showing that the act of going and learning something new is changing your brain and changing the way you process things, which will change the way you actually see the world," he says.

—Catherine Caruso

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GARY JOHN NORMAN *GETTY IMAGES*

NEWS

This Is Your Brain on Poverty

Data visualizations highlight the surprising connections between income and brain structure

Recently I listened to an excellent podcast series on poverty in the U.S. by WNYC called "Busted: America's Poverty Myths." One message that stuck with me is just how many factors the poor have working against them—factors that, if you're *not* poor, are all too easy to deny, disregard or simply fail to notice. In an article entitled "Brain Trust" in the March 2017 issue of *Scientific American*, neuroscientist Kimberly G. Noble highlights one such invisible, yet very real, element of poverty: its effect on brain development in children.

When we consider such a complex topic, any sort of data-driven approach can feel mired in confounding factors and variables. After all, it is not as if money itself has any impact on the structure or function of one's brain; rather it is likely to be an amalgamation of environmental and genetic influences accompanying poverty, which results in an overall trend of relatively low achievement among poor children. By definition, this is a multifaceted problem in which correlation and causation seem virtually impossible to untangle. Nevertheless, Noble's laboratory is tackling this challenge with the best scientific tools and methods available.

First, it is essential to define the problem: In what specific ways does poverty impact brain function? To address this question, Noble recruited some 150 children from various socioeconomic backgrounds and used standard psychological testing methods to evaluate their abilities in several cognitive areas associated with particular parts of the brain. As outlined in the accompanying graphs, the relationships are clear, especially in terms of language skills.

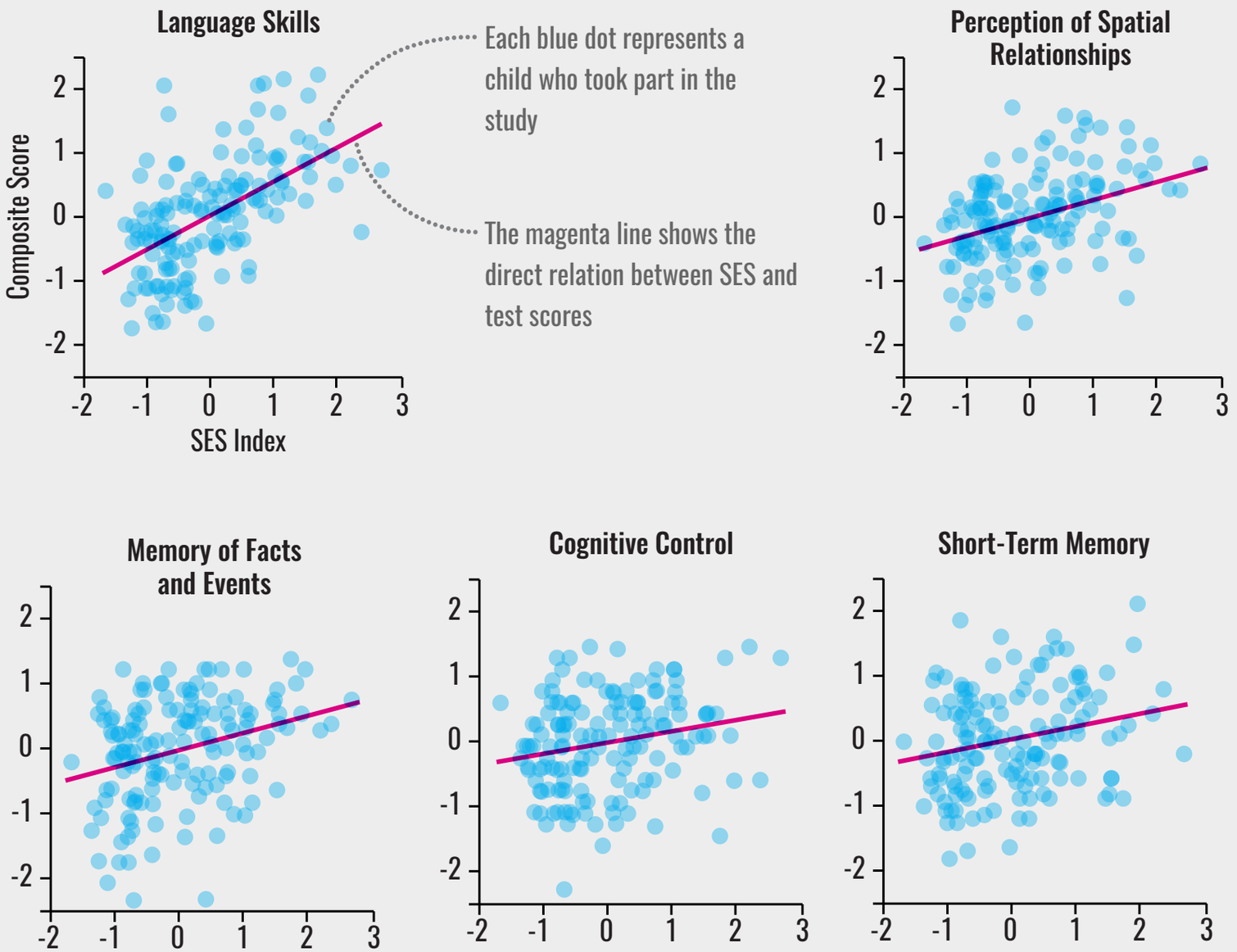
Although the data represented are fairly convincing, they are also incomplete. To demonstrate the physical effects of poverty on the brain, we must examine the organ itself. To this end, Noble's lab scanned the brains of about 1,100 children and adolescents and found clear structural differences based on family income. Remarkably, their results showed that those children falling on the poorer end of the lowest income bracket suffer exponentially severe losses in brain development.

Of all the social issues we face as a country, poverty often feels especially overwhelming, and these kinds of research findings can exacerbate that sense of intractability. But Noble's experiment may provide support for one potential path forward. I encourage you to read the full article at www.scientificamerican.com/magazine/sa to learn more.

—Amanda Montañez

Wealth Effect

Children tended to perform better on various cognitive skills when socioeconomic status (SES) was higher. SES was the factor that explained nearly a third of the difference in performance on language tasks between children from high- and low-income homes, whereas it demonstrated a smaller but still significant portion for other cognitive measures.



SOURCE: "SOCIOECONOMIC GRADIENTS PREDICT INDIVIDUAL DIFFERENCES IN NEUROCOGNITIVE ABILITIES," BY KIMBERLY G. NOBLE ET AL., IN *DEVELOPMENTAL SCIENCE*, VOL. 10, NO. 4; JULY 2007. CREDIT: AMANDA MONTAÑEZ

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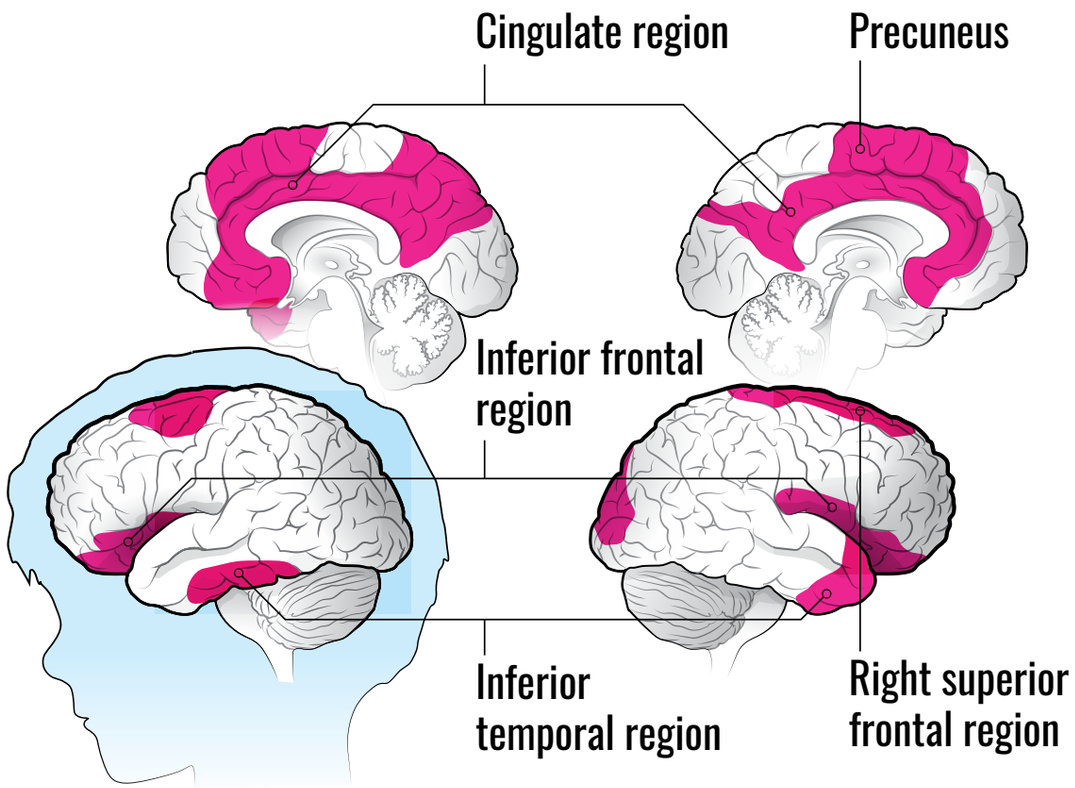
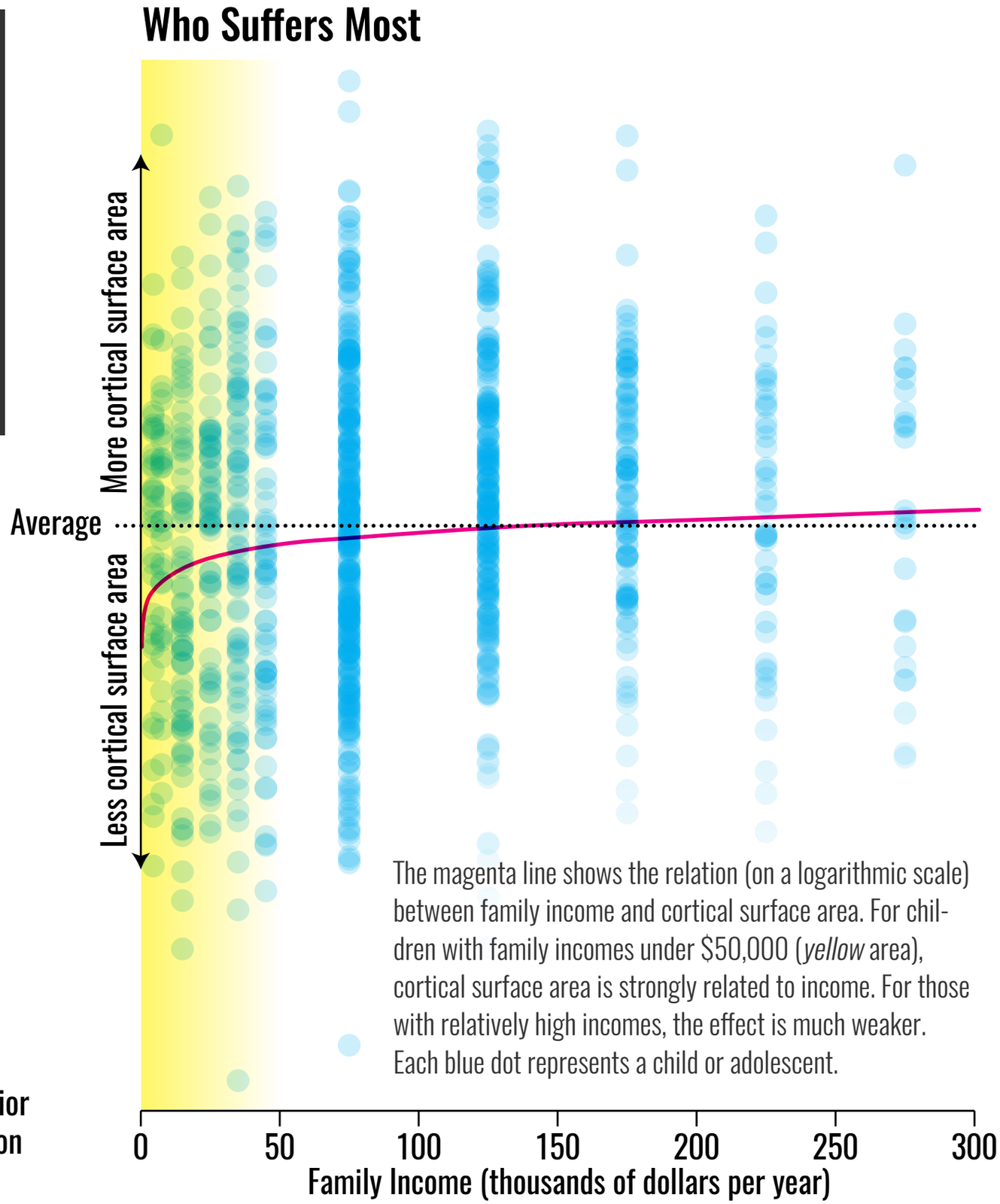
A Brain on Poverty

The travails of an impoverished upbringing reduce the surface area of some parts of the cortex more than others. The affected regions (*magenta*) participate in various forms of mental processing. The researchers demonstrated the connection by plotting collected measures of the affected regions (referred to as the cortical surface area) by socioeconomic status.

Areas of Vulnerability



Who Suffers Most



The magenta line shows the relation (on a logarithmic scale) between family income and cortical surface area. For children with family incomes under $50,000 (*yellow* area), cortical surface area is strongly related to income. For those with relatively high incomes, the effect is much weaker. Each blue dot represents a child or adolescent.

SOURCE: "FAMILY INCOME, PARENTAL EDUCATION AND BRAIN STRUCTURE IN CHILDREN AND ADOLESCENTS," BY KIMBERLY G. NOBLE ET AL., IN *NATURE NEUROSCIENCE*, VOL. 18: MAY 2015. CREDIT: TAMI TOLPA (*BRAIN ILLUSTRATIONS*) AND AMANDA MONTAÑEZ (*GRAPH*)

Goliath birdeater spider

RYAN SOMMA *FLICKR* (CC BY 2.0)

NEWS

The Genius of Pinheads: When Little Brains Rule

Bigger brains are not always better

The Samoan moss spider, the world's smallest arachnid at a third of a millimeter, is nearly invisible to the human eye. The largest spider in the world is the goliath bird eater tarantula, which weighs 142 grams and is about the size of a dinner plate. For reference, that is about the same difference in scale between that same tarantula and a bottlenose dolphin.

And yet the bigger spider does not act in more complex ways than its tiny counterpart. "Insects and spiders and the like—in terms of absolute size—have among the tiniest brains we've come across," says William Wcislo, a scientist at the Smithsonian Tropical Research Institute in Panama City. "But their behavior, as far as we can see, is as sophisticated as things that have relatively large brains. So then there's the question: How do they do that?"

No one would argue that a tarantula is as smart as a dolphin or that having a really big brain is not an excellent way to perform complicated tasks. But a growing number of scientists are asking whether it is the only way. Do you need a big brain to hunt elusive prey, design complicated structures or produce complex social dynamics?

For generations scientists have wondered how intelligent creatures developed large brains to perform complicated tasks. But Wcislo is part of a small community of scientists less interested in how brains have grown than how they have shrunk and yet shockingly still perform tasks as well as or better than similar species much larger in size. In other words, it is what scientists call brain miniaturization, not unlike the scaling down in size of the transistors in a computer chip. This research, in fact, may hold clues to innovative design strategies that engineers might incorporate in future generations of computers.

Scientists interested in brain miniaturization often refer to something called Haller's rule, proposed by German neuroscientist Bernhard Rensch and named for the 18th-century father of physiology, Albrecht von Haller. It holds that smaller creatures will have smaller brains but that the ratio of brain to body size will actually go up. And what is amazing is that few if any creatures on earth violate this rule. "It's extremely general, and it's been known for a long time. And there seem to be no good ideas as to why in the world it's true," says William Eberhard, a spider researcher and frequent collaborator with Wcislo, who also works at the Tropical Research Institute.

Imagine packing for a trip with a massive suitcase and then learning that the plane will accept only luggage half that size. The trip is the same, but the space just got tight, so you will have to be more efficient, and your bag might be bursting at the seams. The same thing happens to some of Eberhard's smaller spiders. "Their brains were not staying in the right parts of their body. In the tiny ones they were going into the legs, and the sternum was bulging out, and it was full of brain. Their bodies were being deformed by these brains," he says.

The comparison of scale in this spider world boggles the mind. Take Eberhard's favorite group of creatures, orb weaver spiders. The largest he has worked with weighs around three grams, whereas the smallest weighs 0.005 milligram—roughly 600,000 times as small as its cousin. For perspective, imagine a normal adult man standing next to a giant who stood 400 kilometers tall and weighed more than 300 blue whales. The giant's brain alone would weigh 910,000 kilograms.

So would such a giant be more intelligent than a human? If the scaling princi-

ples hold from the world of spiders, the answer is no, as can be seen by looking closely at the webs they spin.

As a spider constructs a web, it must continually make decisions, finding the most efficient places to attach each thread. And although they are exceptional architects, they do make mistakes—and those mistakes are pretty consistent over time. So Eberhard used these web-making mistakes as a proxy for cognitive capacity. Knowing the incredible costs of having a tiny body and thus an outsize brain, he expected to see that cost reflected in their webs. The smaller spiders should make more mistakes.

Shockingly, they do not. In fact, species to species and even within the species, the number of mistakes was exactly the same. Then a student of Eberhard's tested the little critters, forcing them to build in a constrained environment—inside a piece of tubing about the diameter of a large air-rifle BB. Again, the spiders made the same number of miscalculations, even as newly born nymphs. The same seems to be true for parasitic wasps, which span from the massive tarantula hawk to a fairy wasp that is smaller than a single-celled paramecium. The latter have truly minuscule brains but are equally as adept at locating and ambushing prey. "We haven't yet found any behavioral costs of having a totally tiny brain," Wcislo says.

How could such a tiny brain perform as well as a bigger one? Through vicious, cutthroat evolutionary efficiency.

How could such a tiny brain perform as well as a bigger one? Through vicious, cutthroat evolutionary efficiency. Some tiny creatures actually have shrunken brain cells with dramatically shorter connecting axons, the wirelike extensions from neurons. But even then, there is a lower limit—a cell cannot get smaller than its nucleus (although some beetles may simply jettison the nucleus altogether). And if axons get too short, they start interfering with one another like tangled electrical cabling.

So having a halfway-decent brain is a tough job for small invertebrates. What does this mean for us larger creatures? It turns out that Haller's rule does not care if you are a spider, wasp, bird or even a human. As animals evolve to become smaller because of a change in climate or other selective pressures, their brain demands an ever higher percentage of energy and real estate in their body.

One species of salamander that, like insects, can vary wildly in size has evolved a thinner skull to make room for its brain. And although it is not yet clear how all this applies to humans, we do know that human brains have shrunk over the past 10,000 years. Perhaps rather than becoming less intelligent, our ancestors' brains were just becoming more efficient.

Diego Ocampo, a biologist currently finishing his Ph.D. at the University of Miami, took a survey of more than 70 bird species and found that they perfectly follow Haller's rule, with the smallest ones having proportionally larger brains. But when he looked at individual groups, he noticed hummingbirds had their own supercharged version of the rule. Take two species of hummingbird. The violet sabrewing, a sizable bird at 12 grams, is about 2.4 percent brain. Meanwhile the striped-throated hermit, which is a fifth the size, is 4.8 percent brain. Compared with other creatures, these numbers are oddly low. Far bigger birds that he sampled, such as thornbills, have a brain that takes up an ungainly 7 percent of their body.

It is as if the hummingbirds as a group have come up with a far more efficient type of brain than other birds—a slight bending of Haller's rule. And if that was not enough, the hermit, far from being a simpleton, actually demonstrates the most complex behaviors. Whereas the sabrewing tends to sit and guard a single plant, the hermit memorizes complex lines to follow through the forest to find food.

What if birds have unlocked some kind of ultraefficient brain design that allows them to do more with less? Certainly this would explain some of the stupendous abilities observed in, say, African grey parrots, which can identify shapes and even count, as well as corvids, which have an equivalent number of neurons to some primates and, it is suggested, may even be self-aware. Do not forget octopuses, which have very primitive brains and yet perform tasks that rival those of dogs.

Lars Chittka, who studies bee behavior and intelligence at Queen Mary University of London, flips these questions about animal smarts on their head. It is not that they require large brains to do complicated things, he says, it is that complicated behavior really does not require much brainpower. "The task that requires a large brain hasn't been discovered yet," he says. "You can do a whole lot with very little brains." Some wasps, he says, are able to recognize the faces of every other wasp in their communities. But when he looks at their brain, there is nothing to explain such an impressive ability. Chittka suggests facial recognition may have evolved from simpler abilities, such as recognizing food sources. And given that bees have complex social interactions, symbolic language and excellent spatial memory, there is not really much to separate their intelligence from that of, say, a rodent.

Still, it stretches credibility to compare two species from vastly different parts of the animal kingdom and even harder to understand how physiology corresponds to specific behaviors. But, Eberhard says, any animal that has been pushed "up against the wall of Haller's rule" by evolving to a smaller size while maintaining complicated behaviors is bound to have come up with a few interesting ways to streamline its brain.

Wcislo compares large animals such as whales and perhaps humans, with the large Apple IIe computers that sat on so many desks in the 1980s and revolutionized personal computing. They were powerful tools, but there was lots of wasted space and ex-

cess heat production. Now compare that with modern iPhones, and you see the power of miniaturization.

So maybe it is not surprising that Wcislo's work has attracted the attention of Silicon Valley. His oldest and most devoted funder is Frank Levinson, a venture capitalist and founder of the fiber-optics giant Finisar. To explain why he started investing in bug research, Levinson describes the time he watched a pair of male butterflies near his home compete for a female's attention, ducking and weaving around a bush. "The best chip out of Intel can't fly, can't dance, can't romance a woman, can't dogfight," he says. "I don't know anything in silicon that could do anything remotely as complex as this."

If tiny animals have learned to do more with less, what is stopping electronics from doing the same?

Levinson says electronics companies today are obsessed with artificial intelligence—how to make machines more humanlike—at the same time that the increase in computing speeds seem to be slowing down for the first time since the 1970s. So, Levinson says, there is a huge need to both understand how intelligence works and make circuits smaller and more efficient. In other words, more insectlike.

Insects provide plenty of examples of high-performing computational machines. Take Wcislo's latest obsession, nocturnal sweat bees that live under a jungle canopy with 10 to 20 times less light than on a moonless night. It is so dark that the laws of physics say there are not enough photons to distinguish a visual signal from background noise. "How the hell do they see?" Wcislo says. "They should not be able to see." It seems their tiny brain acts as a filter for the image, like night-vision goggles, extracting an image out of the surrounding darkness. He is also training ants to walk through mazes and then comparing their brain with those of other ants living less intellectually challenging lives. These are the kinds of questions that may suggest cutting-edge materials and designs to allow computers to shrink as fast as animal brains have.

At the end of the day, insect brains offer more than just incredible efficiency—they also offer simplicity. Investigations into artificial human intelligence are tricky, partly because the human brain is inordinately complex. But as these scientists are finding, there is much you can do with a very small, efficient brain. Perhaps there is more programmers can learn from them as well.

"Silicon Valley is always looking for those new niches," Levinson says. "One interesting place to look is with [Wcislo] and the guys studying something as simple as ants and bees and spiders—and see what they can tell us about thought processes and learning."

—Erik Vance

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NEWS

Your Brain Remembers Languages You Think You Forgot

Kids adopted in a new country have an advantage in learning their native tongue as adults, even if they have not heard it since birth

New evidence suggests that the earliest traces of a language can stay with us into adulthood, even if we no longer speak or understand the language itself. And early exposure also seems to speed the process of relearning it later in life.

In the new study, recently published in *Royal Society Open Science*, Dutch adults were trained to listen for sound contrasts in Korean. Some participants reported no prior exposure to the language; others were born in Korea and adopted by Dutch families before the age of six. All participants said they could not speak Korean, but the adoptees from Korea were better at distinguishing between the contrasts and more accurate in pronouncing Korean sounds.

"Language learning can be retained subconsciously, even if conscious memories of the language do not exist," says Jiyoun Choi, postdoctoral fellow at Hanyang University in Seoul and lead author of the study. And it appears that just a brief period of early exposure benefits learning efforts later; when Choi and her collaborators compared the results of people adopted before they were six months old with results of others adopted after 17 months, there were no differences in their hearing or speaking abilities.

"It's exciting that these effects are seen even among adults who were exposed to Korean only up to six months of age—an age before which babbling emerges," says Janet Werker, a professor of psychology at the University of British Columbia, who was not involved with the research. Remarkably, what we learn before we can even speak stays with us for decades.

—Jane C. Hu

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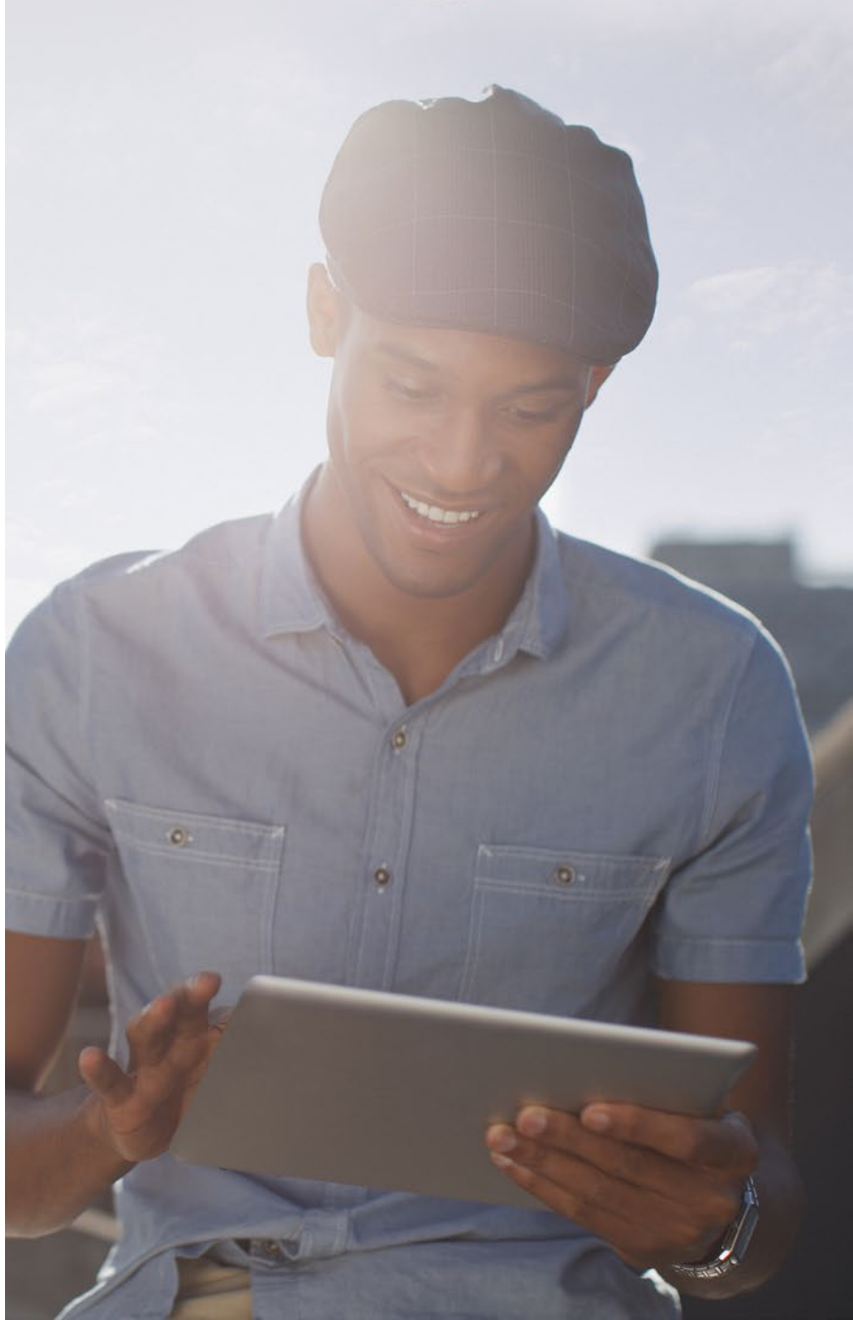

STEVEN GSCHMEISSNER *GETTY IMAGES*

NEWS

Meditation's Calming Effects Pinpointed in the Brain

A new mouse study reveals a set of neurons that may point to physiological roots for the benefits of breathing control

During yoga pranayama exercises, people practice controlling the breath, or prana, to induce a state of calm and focus. Paying attention to breathing and slowing down respiration constitute a core component of many mindfulness practices. Research suggests the practice has multiple benefits—it induces an overall sense of well-being while reducing anxiety and improving sleep.

But what exactly is going on in the brain during meditation? Imaging studies of humans have shown that brain regions involved in mind wandering, attention and emotion play a part in various stages of mindfulness practice. A new mouse study, published recently in *Science,* shows that neurons in the brain stem may also mediate the link between breathing and inducing a state of meditative calm.

The basis for the new study dates back to 1991, when a group of neuroscientists at the University of California, Los Angeles, discovered the pre-Bötzinger complex, an area containing neurons that fired rhythmically in time with each breath. "Quite different from the cardiac pacemaker, the breathing pacemaker has a whole variety of different rhythms—for example, a yawn or a sigh or a gasp," says study co-author Mark Krasnow, a biochemistry professor at Stanford University. Rather than simply providing air to your lungs, these types of breaths are also associated with social and emotional signals.

Recent evidence suggests that the pre-Bötzinger complex can control different breathing behaviors. In a study published last year in *Nature,* Krasnow and his colleagues reported on a subset of neurons within this brain region that is solely responsible for generating sighs. When the researchers stimulated these neurons in mice, they sighed continuously. But when the team removed those nerve cells, the animals kept breathing, never sighing. Now the team has uncovered a separate group of neurons in this area that appear to have another specific function: regulating states of calm and arousal.

Krasnow's team genetically engineered mice to remove a specific subset of neurons that contains two genes: *cadherin 9* (*Cdh9*), a gene that is expressed in the pre-Bötzinger complex, and *developing brain homeobox protein 1* (*Dbx1*), which prior studies had demonstrated are necessary for respiration—without it, mice do not breathe.

When the team removed these *Cdh9/Dbx1* neurons from mice, the animals still breathed normally with one slight difference: breaths came more slowly than in normal mice. The rodents were also unusually calm—they spent less time exploring their surroundings and more time sitting still. "We were totally surprised," says study co-author Kevin Yackle, a professor at the University of California, San Francisco, who conducted the study while he was a postdoc at Stanford. "It certainly wasn't something we expected to find."

The researchers also discovered these neurons form connections with the locus coeruleus, another area in the brain stem involved in modulating arousal and emotion. "[One] thing that's interesting about this, and surprising, is that this small group of neurons is not involved in producing the inspiratory rhythm per se," says Jeffrey Smith, a neuroscientist at the National Institute of Neurological Disorders and Stroke, who was not involved in the study. Smith, along with one of the recent *Science* study's co-authors, neurobiologist Jack Feldman of U.C.L.A., discovered the pre-Bötzinger complex. "It's now becoming apparent that there's a lot of structural and

functional complexity to the pre-Bötzinger complex itself that we hadn't really anticipated."

Evidence from human research also suggests that meditation and respiration are closely connected. In another study, for example, Antoine Lutz, a scientist who researches the neurobiology of meditation at the French National Institute of Health and Medical Research, and his colleagues at the University of Wisconsin–Madison discovered that long-term meditators develop slower breathing patterns than those who did not practice on a regular basis. The slower breathing in long-term practitioners may "activate this ascending pathway less," says Lutz, who was not involved in the *Science* study. "Maybe it's a signature of a different level of stress."

According to Lutz, the findings from the *Science* paper raise the possibility that "any form of practice—from yoga pranayama to meditation—that is actively manipulating respiration might be using this pathway to regulate some aspects of arousal." He points out, however, that this pathway may not be as relevant for forms of meditation that do not involve directly controlling respiration. For example, in some types of mindfulness training, individuals simply observe their breath rather than control it.

"Breathing is about staying alive on one level, but it's also connected to emotional life," says Christopher Del Negro, a neurophysiologist at the College of William & Mary, who was not involved in the work. The studies showing that different neural populations in the pre-Bötzinger complex can also control sighing and regulate arousal "begin to break that next level of not just talking about breathing for physiology but breathing for emotional well-being," he adds.

Understanding how the brain controls breathing could also help develop new therapeutic targets to treat conditions such as anxiety, panic disorders and arousal-related sleep disorders. "[Cardiologists] have ways of pharmacologically controlling the heart rhythm," Yackle says. "But a similar type of pharmacological approach for breathing doesn't exist, and I think it could be important in multiple fields of medicine."

Before that happens, however, neuroscientists will first need to uncover how this brain region works in people. Researchers have found a pre-Bötzinger complex in humans, but its anatomy and physiology are much less understood. For now Krasnow, Yackle and their colleagues plan to investigate the other populations of neurons in the breathing pacemaker of rodents to see what other functions they might find. The present study, though, holds promise of eventually furnishing at least a partial window on the physical underpinnings of an ancient practice.

—Diana Kwon

Mind over Meal:

Does Weight-Loss Surgery Rewire Gut-Brain Connections?

New evidence hints that bariatric surgery changes the dialogue between bowel and brain

By Bret Stetka

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For Teresa, the first plate of scrambled eggs was a transcendent experience. The 41-year-old Stanford University Medical Center nurse coordinator had completely lost her appetite in the days after her surgery. She ate, but only liquids and only at her surgeon's request. Yet when her interest in eating returned, it was as though something about her relationship with food had fundamentally changed.

The eggs, Teresa's first solid meal in four weeks, were a revelation: simple, soft and buttery. To her surprise, they constituted a completely satisfying meal. Gone was the desire for sweets and excessively salted savories. Her once beloved french fries and rich desserts no longer enticed her. Her desire to eat was back, but for the first time in her life eating "right" came easy.

Teresa had undergone a sleeve gastrectomy, one of a variety of procedures—known as bariatric surgeries—that manipulate the stomach and intestines to promote weight loss. Yet more than shedding pounds, which she did, it was the complete change in cravings that Teresa considers the most surprising result of her 2012 operation.

She had struggled with her weight since childhood. Years of hormone therapy while trying to get pregnant did not help, nor did pregnancy itself. "Before I knew it, I was 270 pounds," Teresa recalls. "And I just couldn't get the extra weight off despite trying everything: every diet, lots of exercise." The surplus pounds also made it hard to manage a toddler. "I couldn't keep up with my son," she says.

A sleeve gastrectomy can shrink the stomach from the size of a football to that of a banana, roughly 15 percent of its original size. One year later—after months of eating healthier and eating less—Teresa was down to 150 pounds. "That was actually even low for me," she says, "but the surgery really changed how I ate."

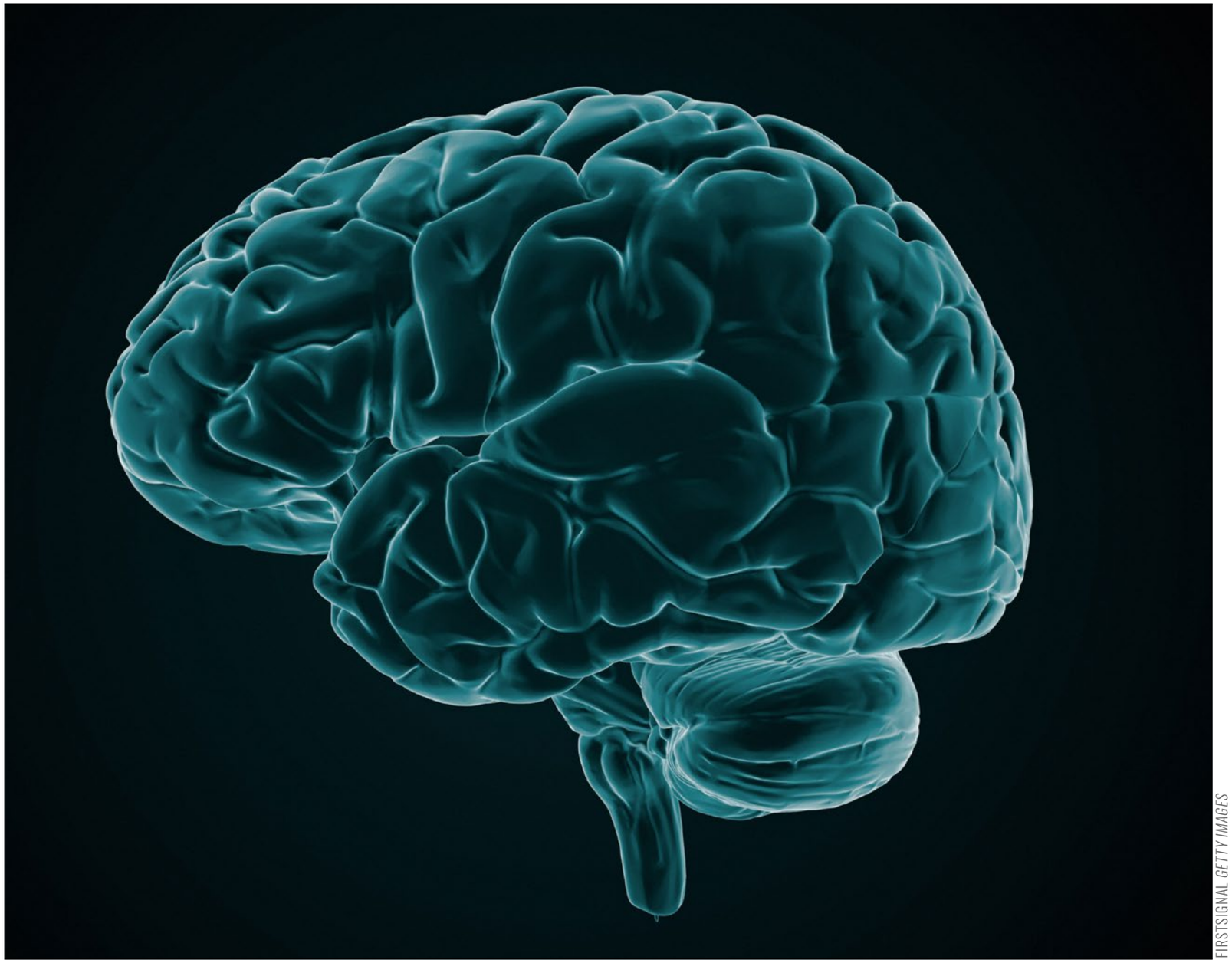
Since the 1960s, when these techniques were introduced, doctors have considered bariatric surgery primarily a mechanical fix. A smaller stomach, the reasoning went, simply cannot hold and process as much

Bret Stetka is a writer based in New York City and an editorial director at Medscape (a subsidiary of WebMD). His work has appeared in *Wired*, NPR and the *Atlantic*. He graduated from the University of Virginia School of Medicine in 2005.

IN BRIEF

The Skinny on Surgery

- Doctors have long suspected that bariatric surgeries help patients lose weight by reducing the size of the stomach—but new work suggests other mechanisms are involved.
- After the procedure, brain areas involved in communicating with the gut become hyperactive compared with their earlier activity.
- In addition, these interventions change the microbial populations living within digestive systems in ways that could further adjust signaling along the gut-brain axis and contribute to new, healthier eating habits.



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food. Patients get full faster, eat less and therefore lose weight.

This idea is in part true. But now scientists know that it is not nearly that simple. Teresa's weight loss was in all likelihood caused by the drastic change in how her gut speaks to her brain, and vice versa. The procedure had indirectly spurred new neural connections, changing how she thought about and craved food.

Recent science has revealed that appetite, metabolism and weight are regulated through a complex dialogue between bowel and brain—one in which mechanical influences, hormones, bile acids and even the microbes living in our gut all interact with labyrinthine neurocircuitry. Bariatric surgery, scientists are discovering, engages and may change all these systems. In the process, it is helping researchers map how this complicated interplay manipulates our eating behaviors, cravings and frenzied search for calories during starvation. This work could also reveal new targets—including microbes and possibly the brain itself—that render the risky surgical procedure obsolete altogether.

Brain Meets Bowel

We have all felt the physical effects of the gut-brain communion: the gastric butterflies that come with love, the rumbles that arise before delivering a speech. These manifestations result from the brain signaling to the gastrointestinal tract, both through hormones and neuronal signals.

Conversely, the gut can send signals back to the brain, too. In fact, coursing through our abdomen is the enteric nervous system, colloquially known as the second brain. This neural network helps to control food diges-

tion and propulsion through the 30 feet of our gastrointestinal tract. It also communicates directly with the brain through the vagus nerve, which connects the brain with many of our major organs.

Two primary gut-brain pathways regulate appetite. Both systems involve a small, central brain region called the hypothalamus, a hotbed of hormone production that helps to monitor numerous bodily processes.

The first system comes into play during fasting. The stomach secretes the hormone ghrelin, which stimulates a region within the hypothalamus called the arcuate nucleus. This structure then releases neuropeptide Y, a neurotransmitter that, in turn, revs up appetite centers in the cerebral cortex, the outer folds of the brain, driving us to seek out food. In anticipation of mealtime, our brain sends a signal to the stomach via the vagus nerve, readying it for digestion. "This can occur simply at the sight, smell or thought of food," says Mayo Clinic gastroenterologist and obesity expert Andres Acosta Cardenas. "Our brain is preparing our body for a meal."

The second gut-brain pathway suppresses our appetite. As we eat, several other hormones, including leptin and insulin, are secreted from fat tissue, the pancreas and the gastrointestinal tract. Separately, these hormones play many roles in digestion and metabolism. Acting together, they signal to another area of the hypothalamus that we are getting full. Our brain tells us to stop eating.

The appetite and satiety loop constantly hums along. Yet hunger pathways also interact with brain regions such as the amygdala, involved in emotion, and the hippocampus, the brain's memory center. Hence, our "gut feelings" and "comfort foods" are driven more by moods than mealtimes and nostalgic recollections of Grandma's rhubarb pie. As a result of higher thinking processes, food now has context. Food is culture. As playwright George Bernard Shaw put it, "There is no sincerer love than the love of food."

Then there is the hedonistic thrill of sitting down to a meal. Eating also lights up our reward circuitry, pushing us to eat for pleasure independent of energy needs. It is this arm of the gut-brain axis that many scientists feel contributes to obesity.

Neuroimaging work confirms that, much like sex, drugs, gambling and other vices, food can cause a surge of dopamine release

PETER DAZELEY *GETTY IMAGES*

in the brain's reward circuitry. This neurotransmitter's activity serves as a powerful motivator, one that can reinforce dining for its own sake rather than subsistence. Researchers have found that for rats, sweetness surpasses even cocaine in its desirability. In humans, psychiatrist Nora Volkow, director of the National Institute on Drug Abuse, has confirmed what chocolate lovers everywhere already know: food's effects on the reward system can override fullness and motivate us to keep eating. Such findings hint at a neurobiological overlap between addiction and overeating, although whether eating can be an outright addiction remains a controversial question.

The Surgical Solution

Thanks to the flow of messenger hormones and neurotransmitters, our mind and stomach are in constant communication. Disrupting this conversation, as bariatric procedures must do, will therefore have consequences.

Research has shown that in the days and weeks after bariatric surgery, sugary, fatty and salty foods become less palatable (as Teresa discovered). One study, published in 2010 by Louisiana State University neurobiologist Hans-Rudolf Berthoud, found that rats lost their preference for a high-fat diet following gastric bypass surgery. In the 1990s multiple research teams had reported that after such surgery, patients often lose the desire to consume sweet and salty foods. More recently, a 2012 study by a team at Brown University found that adult patients had significantly reduced cravings for sweets and fast food following bariatric surgery. Similar findings in adolescent surgery patients also appeared in a 2015 study.

The alteration in cravings and taste may be caused by changes in the release and reception of neurotransmitters throughout the gut-brain system. In 2016 Berthoud and his colleagues found that in the short term—around 10 days postprocedure—bariatric surgery in mice caused additional meal-induced neural activity in brain regions known to communicate with the gut compared with brain activity before the surgery. Specifically, the boost in activity was seen in a connection leading from stomach-sensing neurons in the brain stem to the lateral parabrachial nucleus, part of the brain's reward system, as well as the amygdala.

An expert in this area is biochemist Richard Palmiter of the University of Washington. In a 2013 study published in *Nature*, Palmiter's group used complex genetic and cell-stimulation techniques—including optogenetics, a means of controlling living tissue using light—to activate or silence specific neurons in the brain stem parabrachial nucleus pathway in mice. He found that engaging this circuit strongly reduced food intake. But deactivating it left the brain insensitive to the cocktail of hormones that typically signaled satiety—such that mice would keep eating.

Palmiter's work suggests that engagement of the brain stem parabrachial pathway helps us curb our appetite. Because it is this same pathway that becomes unusually active postsurgery, it is probable that the hyperactivation Berthoud discovered is part of the gut-brain's effort to assess satisfaction postsurgery. As he puts it, "the brain must relearn how to be satisfied with smaller portions."

In other words, bariatric surgery is certainly a mechanical change: with less space, the body needs to adjust. Still, there is clearly more to the story. After the procedure, more undigested food may reach the intestine, and, Berthoud speculates, it would then trigger a hormonal response

that alerts the brain to reduce food intake. In the process, it would alter the brain's activity in response to eating. If he is correct, the surgery's success—at least in the short term—may have as much to do with its effects on the gut-brain axis as it does on the size of a person's stomach.

The Microbial Mind

There is *another* player in the complex communications of mind and gut that might explain bariatric surgery's effects. Experts have implicated the microbiota—the trillions of single-celled organisms bustling about our digestive system—in countless disorders, including many that affect the brain. Our co-denizens and their genome, the "microbiome," are thought to contribute to autism, multiple sclerosis, depression and schizophrenia by communicating with the brain either indirectly via hormones and the immune system or directly through the vagus nerve.

Research by gastroenterologist Lee Kaplan, director of the Massachusetts General Hospital Weight Center, suggests that the microbiota may play a role in obesity. In a study published in 2013 in *Science Translational Medicine*, Kaplan and his colleagues transferred the gut microbiota from mice that had undergone gastric bypass surgery to those that had not. Whereas the surgery group lost nearly 30 percent of their body weight, the transplanted mice lost a still significant 5 percent of their body weight. (Meanwhile a control group that did not have surgery experienced no significant weight change.) The fact that rodents could lose weight without surgery, simply by receiving microbes from their postoperative fellows, suggests that these microbial populations may be at least partly responsible for the effectiveness of bariatric procedures.

A similar study, published in 2015 by biologist Fredrik Bäckhed of the University of Gothenburg in Sweden, found that two types of bariatric surgery—the Roux-en-Y gastric bypass and vertical banded gastroplasty—resulted in enduring changes in the human gut microbiota. These changes could be explained by multiple factors, including altered dietary patterns after surgery; acidity levels in the gastrointestinal tract; and the fact that the bypass procedure causes undigested food and bile (the swamp-green digestive fluid secreted by the liver) to enter the gut farther down the intestines.

As part of the same research, Bäckhed and his colleagues fed mice microbiota samples from obese human patients who either had or had not undergone surgery. All the rodents gained varying degrees of body fat, but mice colonized with postsurgical microbiota samples gained 43 percent less.

How might changes in our gut's flora alter their interactions with the gut-brain axis and affect weight? Although the answer is still unclear, there are a few promising leads.

Specific gut microbial populations can trigger hormonal and neuronal signaling to the brain such that they influence the development of neural circuits involved in motor control and anxiety. Bäckhed suspects gut flora after bariatric surgery could have a comparable effect on brain regions associated with cravings and appetite.

The neurotransmitter serotonin could play a special role as well. About 90 percent of our body's serotonin is produced in the gut, and in 2015 researchers at the California Institute of Technology reported that at least some of that production relies on microbes. Change the microbes; change the serotonin production. And that could make quite a dif-

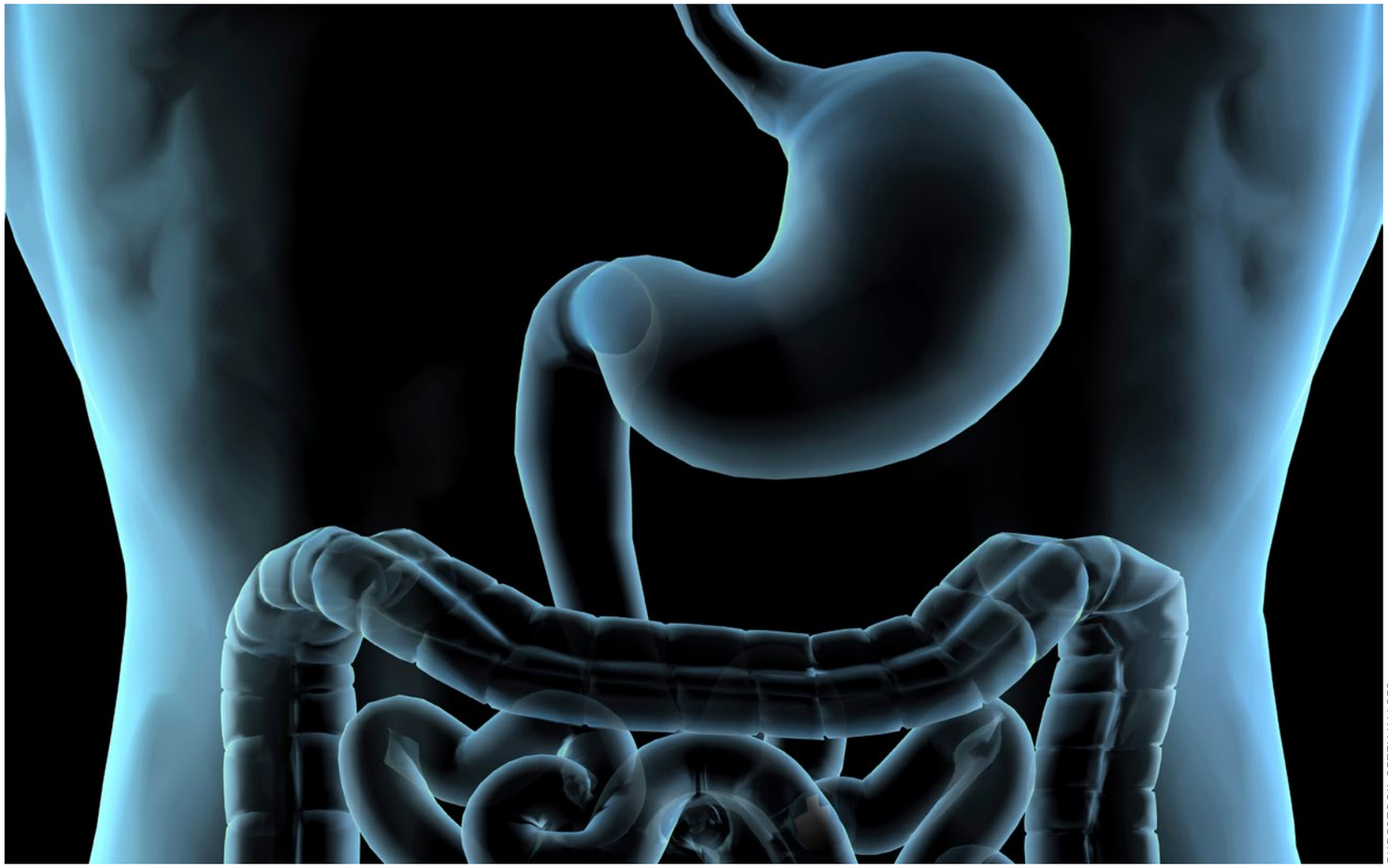
ference because, as numerous studies have confirmed, stimulating the brain's serotonin receptors can significantly reduce weight gain in rodents and humans.

Treating the Gut-Brain Axis

It is a welcome turn of fate that bariatric surgery is illuminating new directions in treating obesity—which affects more than 600 million people worldwide. Some of these avenues could render surgery obsolete or at least reserved for the most extreme cases. Thus, at the forefront of battling excess weight may be hijacking the gut-brain axis.

In 2015, for example, the U.S. Food and Drug Administration approved a device that stimulates the vagus nerve to quell food cravings. A surgeon implants the device, made up of an electrical pulse generator and electrodes, in the abdomen so that it can deliver electric current to the vagus nerve. Although precisely how it works is unknown, the study leading to its approval found that patients treated for one year with this tool lost 8.5 percent more of their excess weight than those without the device.

That approach offers some patients a less invasive alternative to bariatric surgery, but for the moment, vagus nerve stimulators are not as effective as many other obesity therapies. Meanwhile a number of intrepid neurosurgeons are investigating the use of a technique called deep-brain stimulation. Approved for use in Parkinson's disease and obsessive-compulsive disorder, the procedure involves stimulating specific brain regions using implanted electrodes. Although this research is in its infancy, numerous brain regions involved in appetite control are being explored as possible targets.



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The Mayo Clinic's Acosta Cardenas believes that in the future the best approach to treating obesity will be highly personalized. "Obesity is a disease of the gut-brain axis," he says, "but I think we need to identify which part of the axis is abnormal in each patient to personalize treatment. I'm trying to identify which patients have a problem with the microbiome, or hor-

mones, or emotional eating so we can maximize response to treatment."

In 2015 Acosta Cardenas and his colleagues looked at numerous factors potentially related to obesity in more than 500 normal-weight, overweight and obese patients. Among the factors were how quickly the study subjects got full, how quickly their stomachs emptied, hormone levels in response to eating and psychological traits. Acosta Cardenas's findings support the idea that there are clear subclasses of obesity and that the cause and ideal treatment of obesity is most likely unique to each patient. For example, 14 percent of the obese individuals in his study have a behavioral or emotional component that would steer his treatment recommendation away from surgery and medication and toward behavioral therapy. He can also foresee a future in which he might prescribe a probiotic or antibiotic for obesity patients with an abnormal microbiota.

At the moment there is no telling with certainty which perturbations of the gut-brain axis caused Teresa's weight gain. But it is clear that she has benefited from surgery, maintaining her desired weight of 160 pounds for more than four years to date. Her feet do not hurt anymore. She has more energy. She can keep up with her son. And although she admits certain cravings have crept back during the years, they are not as intense as they once were and are far more manageable.

"Before my surgery I had no self-control. I couldn't hold back," Teresa recalls. "Now if french fries show up at the dinner table, I may have a few, but I don't have to deprive myself. I just don't have the drive to eat that way anymore. I will inevitably take half of my meal home." M

MORE TO EXPLORE

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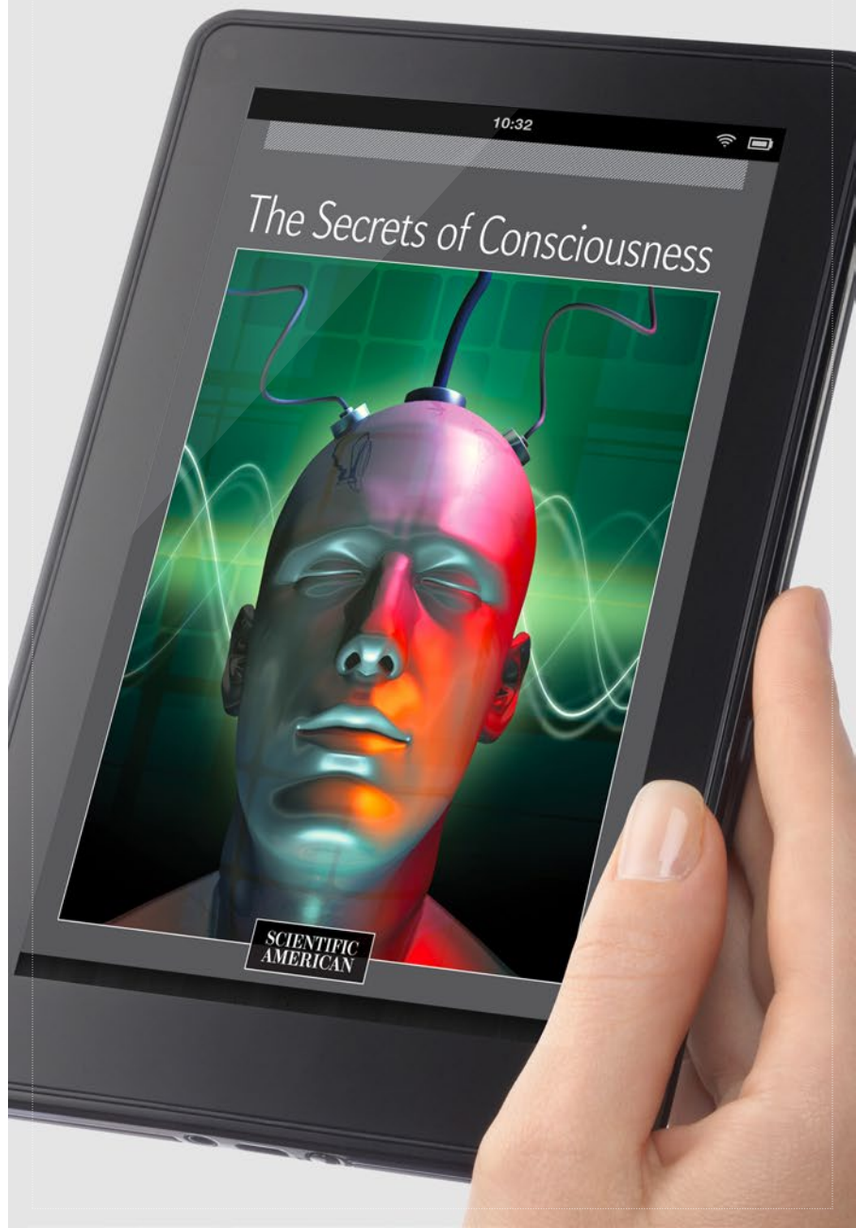

Deciphering the Language of Love

By Sue Johnson

Attachment science is helping couples master communication and connection—and getting through conflict

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Much of the anguish and the elation in our lives begins with a glance, a kiss and then—a lifelong struggle to make sense of the verb *to love*. Patients have faith that their doctor can set a broken bone or offer pills to adjust their blood pressure. But poets, philosophers and psychologists alike have long seen love as intangible and nebulous, beyond our abilities to define. As one young man with whom I worked said, "I don't think anyone has ever had any real idea about this love thing, and you don't either." Love is a many-splendored, *mysterious* thing. How, people wonder, can I or anyone else proffer advice on enigmatic matters of the heart?

In my experience as a researcher and couples therapist, I have encountered many, many people trying to tackle that puzzle. Countless times I have heard: "I don't know what went wrong with my relationship … and I have no idea how to put it right."

In fact, there are real, research-backed ways to help people understand and strengthen love. For several decades now the science of attachment has stirred a quiet revolution. We know, for instance, that patterns of behavior learned in childhood form a template for our adult relationships. At a deeper level we can see the evolutionary and biological richness of love and affection; our connections have measurable effects on our body and health. Perhaps most excitingly, we have studied ways to guide couples toward healthier relationships. In a sense, attachment science, which once focused on the bonds between mother and child, has "grown up" and illuminated myriad powerful predictors for happy couples.

There is a need for that knowledge. In a Pew Research Center survey published in 2012, for example, 84 percent of people saw marriage as a very important life goal—and a Pew survey released in 2010 revealed that most people see love as the basis of marriage. The bulk of people seem to agree with Harvard Medical School psychiatrist Robert Waldinger, who studies happiness,

Sue Johnson is an author, clinical psychologist, researcher, public speaker and developer of emotionally focused therapy. She is also a professor emeritus at the University of Ottawa. In 2016 she received the Order of Canada, a civilian honor.

IN BRIEF

Love Conquers All

- People display characteristic patterns of attachment, often based on relationships with caregivers in childhood, that can shape friendships and romance throughout their life span.
- When someone is "securely attached," he or she feels confident that a loved one is reliable, supportive and responsive.
- Many couples struggle when partners distance themselves emotionally from each other. Emotionally focused therapy helps people bridge these gaps and communicate their needs and feelings.

that the single best recipe for a good life, health and joy is a loving relationship. As a corollary to these beliefs, today relationship troubles are a top reason people seek help from mental health professionals like myself.

Over the years the science of attachment has advanced to the point where it gives us a concrete map to the *practice* of love, to optimizing adult relationships—even very challenging romantic ones. In my own work, I have developed and tested a therapeutic approach that can guide couples toward stronger, more supportive relationships. The latest research confirms and also challenges some of our cherished beliefs about the nature of love. Most important, it does indeed have much to tell us about how to actively shape our romantic relationships for the better.

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A Mother's Love

Consider the bond between parent and child. For much of the 20th century we dismissed children's need for safe connection such that parents routinely dropped their sick children off at the hospital to be cared for by strangers without considering whether this might be traumatizing. Mental health professionals espoused theories that saw unhappy families as victims of *too much* closeness and not enough separation. Separating parent and child was deemed necessary to build strength.

The flaws in this thinking began to appear half a century ago thanks to a series of experiments by psychologists John Bowlby and Mary Ainsworth. In an effort to crack the code of human bonding, they observed interactions between mothers and their infants, then watched how behaviors changed when the two were separated in an unfamiliar environment.

These "strange situation" experiments revealed that some infant-mother exchanges predictably led to calm and positive behaviors in the child, whereas others did not. As revealed in Bowlby's 1969 book *Attachment and Loss*, such scenarios can illuminate patterns in the way children behave that relate to their connection to their

mother. Ainsworth later identified three basic "styles" of attachment that could explain these patterns.

Separation, broadly, causes distress. But for some children, the nature of their bond with their mother is such that when they are left alone, they do not panic. Instead they are curious and can explore a new environment without fear. Parents in these relationships communicated their love and care clearly, and children were comforted by their mother's attentions. Ainsworth called this form of attachment "secure." Secure children display emotional balance, confidence, and an ability to explore and learn. Their sense that their parents provided a safe haven, led to strong children who could connect openly with others as they matured.

But other infants displayed a distinctly different set of behaviors. "Insecure, anxiously attached" children were overwhelmed by the pain and uncertainty of separation. Their parents, when present in the experiments, tended to be less accessible, responsive and engaged. The children's emotional responses were intense. They flipped from anger to panic when calling out to their parent, and when comforted by a mother, they clung to her, as though unwilling to trust that everything was, in fact, okay.

Another group of insecurely attached children showed very little emotion when their mother left or returned. They focused instead on toys and objects. They did not ask for their parent nor did they respond to her comfort. They avoided closeness. Research has since revealed that many of these "avoidant" children are just as upset as their anxious peers but are adept at shutting down their responses, most probably as a consequence of unresponsive or even abusive parenting. They have no expectation of a safe connection.

By the 1980s researchers began to recognize that these patterns could inform adult relationships—including romantic ones. The responses associated with each attachment style become automatic as we grow up and can color the way we think and feel about ourselves in relation to others. For example, we may struggle to trust others if we could not rely on our parents—and a lack of early attention may leave some people unsure whether they are even entitled to another person's care.

Like muscle memory, these patterns kick in when we are vulnerable in romantic relationships. Secure partners tend to have better relationships and better mental health in general. They expect to be responded to and loved. Anxiously attached partners are vigilant for rejection and tend to pursue their partner with intense emotional demands. Avoidant individuals turn away from their partners, especially when they or their lover becomes vulnerable; they dismiss their own and their lover's attachment needs.

Indeed, a longitudinal study, published in 2007 by University of Minnesota psychologists, confirmed the longevity of these patterns. The team worked with 78 young adults who had been studied from infancy. In the study, people who had exhibited secure attachment as one-year-olds were more socially competent in elementary school than people who had lacked secure attachment. That competence in turn predicted better friendships as teenagers—and stronger social connections at age 16 linked to better romantic relationships when the participants were between 20 and 23 years old. Meanwhile other research has made it clear that people exposed to violence and other severe relationship dysfunction in early life not only may develop insecure at-

tachment but are more vulnerable to mental illness and becoming caught in repeat scenarios of abuse as adults.

Entrenched anxious and avoidant styles tend to seed disconnection and relationship distress, which makes it harder for the other partner to stay attuned and responsive. But there is hope. The latest wave of research, of which I have been a part, has investigated ways to modify these patterns and how doing so can truly change someone's life.

Better Together

I began studying attachment science in the 1980s. At that time, I was seeing couples in therapy, and as I became aware of their powerful fears, needs and dilemmas, I began urgently seeking for a way to understand their struggles. Building on the emerging understanding of adult attachment, my colleagues and I developed emotionally focused therapy (EFT) as a short-term therapy grounded in that science.

TARA MOORE *GETTY IMAGES*

To understand how EFT works, we first need to consider a central tenet of attachment research. Namely, the love we feel from another person has an enormous effect on us, both physically and emotionally. Several studies have confirmed that conclusion in recent years.

One pivotal experiment, published in 2006 by James A. Coan, a neuroscientist at the University of Virginia School of Medicine, placed 16 married women in a magnetic resonance imaging machine and subjected them to the threat of electric shock during three different situations: they held their husband's hand, they held the hand of a male stranger or they lay alone in the machine. In each case, a large X appeared on a screen in front of the woman's eyes to warn her that a shock might be coming. The shock was delivered only 20 percent of the time.

Coan found that holding a mate's hand significantly reduced the activation of neural systems in the brain associated with emotional and behavioral threat responses—such as the right anterior insula, superior frontal gyrus and hypothalamus. This act also lessened the amount of pain reported as a result of that shock. Being alone or holding a stranger's hand, however, offered no significant benefit. Furthermore, people who had more supportive marriages, as measured with a questionnaire, seemed to experience the most relief.

Coan's finding is one of various studies that have found that a loved one's presence can modulate neurophysiological responses, such as heart rate and the release of stress hormones. Intriguingly, a series of experiments, published in 2012, revealed that even just imagining an attachment figure can have profound effects. In this work, Emre Selçuk, a psychologist then at Cornell University, and his colleagues encouraged 105 women to determine their attachment style using a questionnaire. These participants then wrote extensively about two vivid and upsetting personal memories. For each story, they created triggers of one to three words and practiced reliving the emotions associated with those moments using just the trigger words. Selçuk next asked the women to trigger those memories while imagining that they were receiving comfort from either their mother or an acquaintance. Then the women rated their emotional response in terms of how positively or how negatively they felt on a scale of 1 to 7, where 1 was not at all, and 7 was extreme. Imagining one's mother—but not an acquaintance—helped people bounce back from the pain and sadness of their unhappy memory, provided they had secure attachment styles. In a second version of this experiment, Selçuk found this recovery also occurred when people looked at a photograph of their mother as opposed to someone else's mother. Both these studies make it clear that we can gain tremendous emotional strength from simply thinking about our attachment figures.

In a third version of the study, Selçuk and his colleagues asked 30 couples to look at a picture of their romantic partner while recalling a difficult experience. As one might expect, securely attached individuals benefited more than others from this exercise. But in an interesting twist, the researchers discovered that partners who reported greater emotional recovery were also healthier, based on observations made one month later. For example, they had less pain and anxiety and were less likely to miss work for health reasons.

That finding was just a correlation, showing physical health and a strong relationship are connected—so it cannot prove that one factor caused the other. Nevertheless, the bulk of attachment research suggests that healthy relationships support healthy lives. As Coan's findings revealed, we feel more at ease in the presence of certain people. Therefore, cultivating those special relationships may help us weather life's uncertainties, which would certainly make us healthier overall.

In that light, our relationships are part of our species' survival code. Secure attachment offers us a potent sense of safety and a way to maintain equilibrium in the presence of danger or threat. These bonds allow us to tolerate and cope with our human frailty. And when we view others as a trusted resource, this perspective fundamentally changes our perception of danger, disaster and pain. The old cliché about how love makes us stronger seems to be accurate.

Helping Couples Connect

The most common problem that relationships face is emotional disconnection. For example, conflict can cause one person to withdraw or stonewall the other. As a result, one partner creates emotional distance from the other. That disconnect triggers the distress of separation—much like the strange situations—which, in turn, can cue a cascade of protest, clinging and pain in the person who feels abandoned. To make matters worse, these situations can be cyclical: emotional distance causes a partner to become enraged or desperate, driving the other farther away.

In the moment, these patterns can look like simple disagreements, often sparked by a perfectly banal problem. But attachment theory suggests that these fights are also dilemmas of disconnection. The threat of emotional isolation can spark either reactive anger (as when a partner declares, "I will make you respond to me") or a numbed shutdown (as in, "I can never please, you so I will just zone out and block you").

In my work, I have found that these meltdowns are more about the pain of emotional disconnection and misguided attempts to reconnect than the conflict per se or even differences in personality. This viewpoint challenges the notion that romantic love is something we simply fall into and out of. Instead attachment science suggests love is *within* our control—we just need to understand how attachment operates.

Thus, the first goal of EFT is to help partners see how they are both caught in a recurring dance of emotional disconnection, triggering each other into aggressively demanding a response or freezing up and shutting down. As a result, they can begin to have a meta-perspective on love, to see how their vulnerabilities are wired into their brain as bonding mammals and to help each other out of these "demon dialogues" that leave them alone and helpless. The second goal is to help partners move, when needing contact or support, into positive experiences of secure connection. That is, we need to show them how to have bonding conversations, in which both partners pinpoint and share specific attachment fears and needs in ways that pull the other close. Partners in these potent bonding conversations may openly share fears of rejection or loneliness and then ask for reassurance in a way that makes it easy for the other to respond. My colleagues and I have observed and then systematically coded these steps in conversation to rate the depth of emotional sharing and how partners reach and respond to each other. Doing so has allowed us to pinpoint transforming moments where successful bonding occurs as well as the moments where this process of attunement and responsiveness gets blocked.

As we noted in a 2013 review, our observations offer many hints as to when and how EFT helps couples to resolve their problems. Not everyone makes progress, but those people who do share important commonalities. For example, we have found that EFT benefits couples who take the time during therapy to delve into and explore their emotional experiences. They disclose more of their perspective. People who soften their tendency to lay blame also show improved relationship satisfaction after therapy. The blend of intimacy, vulnerability and a more forgiving viewpoint seems to be a crucial mix.

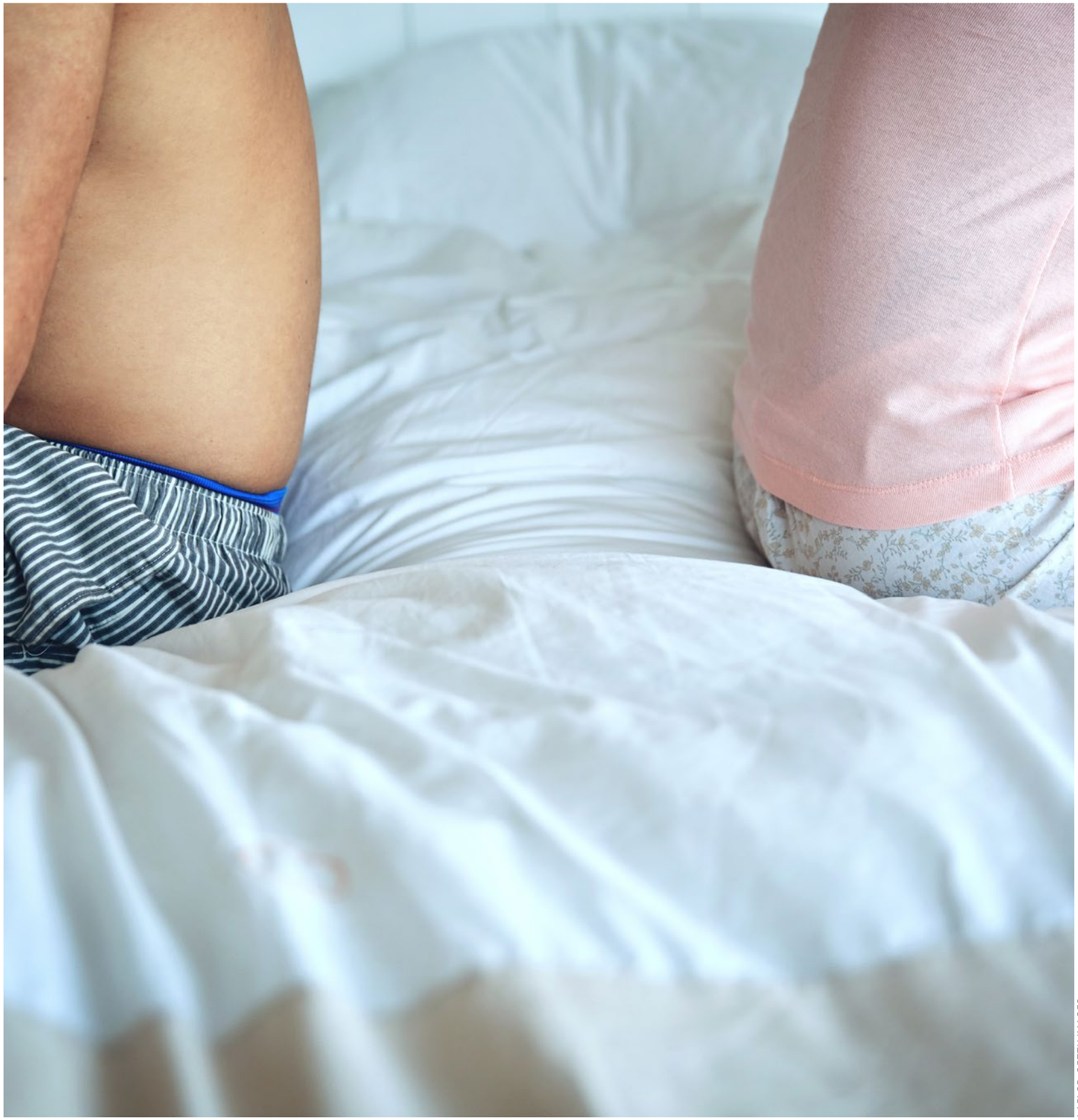
This stage of the process also helps people build up a trio of crucial relationship skills: accessibility, responsiveness and engagement. Accessibility refers to our openness and willingness to turn to and attend to one another. Responsiveness is the abil-

ity to tune into and respond to a partner's emotional signals. Engagement is the ability to stay close and attuned to another's emotions and remain close. In clinical work, we see these qualities captured in the common question: "Are you there for me?" Fundamentally, when people know that the answer to that query is a resounding yes, they are securely attached.

Breaking the Mold

EFT is now the gold standard in tested couple interventions. Though not the only approach for couples therapists, it is unique in its integration with attachment science. Some psychologists make use of behavioral techniques that aim to tackle symptoms of distress, such as mutual blaming, by teaching skills such as active listening and rational negotiation. But few approaches have as strong an evidence base as EFT. To date, researchers have validated it in numerous studies, with many different kinds of couples and relationship problems. Better still, the positive effects of this therapy appear to last across time.

In one of our most interesting findings yet, we discovered that EFT can measurably change someone's attachment style. In



LAFLOR *GETTY IMAGES*

2016 we published a study of 32 distressed couples who attended 20 sessions of EFT. At the start of this endeavor, all the participants said that they were unhappy with their partner. Furthermore, they were chronically emotionally disconnected, meaning they could not safely confide or trust the other person to be there for them when needed.

In addition to requesting the participants to rate themselves on questionnaires, we asked them to discuss a specific relationship conflict at the beginning and end of therapy. Using that information, we determined their attachment style. Although they began with insecure attachment (either anxious or avoidant), by the end of therapy partners rated themselves and each other as securely attached. They were emotionally accessible, responsive and engaged. They also felt that they could get their needs for connection met from each other. A follow-up study, published in this year, found that two years later, these couples still saw their bond as secure and loving.

These studies reveal that the patterns of bonding we learn in early childhood are not immutable. We can change them for the better. Moreover, this process is clearly worthwhile. Our research also suggests that because EFT improves the quality of romantic relationships, it can not only decrease distress caused by conflicts the couple has with each other, it also can build up each partner's resilience to stress. For example, in a 2013 paper we asked 24 couples to participate in brain imaging and made use of the same methods as Coan's hand-holding experiment. We found that before therapy, holding a husband's hand did not buffer women against the dread or pain of an electric shock—but after therapy, it did.

Other teams have confirmed that improvements EFT brings to relationship quality can bolster well-being more broadly. In a 2017 pilot study conducted at the Baltimore VA Medical Center, researchers assigned 15 couples, in which one partner was a military veteran who suffered from post-traumatic stress disorder, up to 36 weeks of EFT. They found that both partners showed better psychological health after therapy and that veterans reported significantly fewer symptoms of their disorder.

EFT gives people the skills to sculpt and keep love. It demonstrates how the new science of attachment can serve as a guide to relationship repair and stability. Although love will always be magical, we can now define the outlines of this emotional bond and know it for what it is. That knowledge is remarkable in itself and part of the great mosaic of findings that science offers us to pursue not just longer but also healthier, happier and more fulfilling lives. Our best relationships, after all, buoy us up amid difficult times. As Mozart is said to have observed, "Love guards the heart from the abyss." That statement is more than just poetic. M

MORE TO EXPLORE

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Listen between the Cries

Researchers try to decipher the hidden messages in babies' wailing

by Janosch Deeg

ALEXANDRA GRABLEWSKI *GETTY IMAGES*

Babies scream for attention—and to get what they want. But, in some cases, their vocalizations may point to medical problems.

Is your baby hungry, sleepy or in pain? A mobile phone app claims to know the answer. The program can tell users why a child younger than six months is crying, according to its developers from the Yun-Lin branch of the National Taiwan University Hospital. To do so, the "Baby Cries Translator" analyzes the frequencies of the baby's wails, looking for small acoustic fluctuations. It then compares the recorded pattern with a database and determines the likely reason for the outburst. The program asks the parents for feedback. It thereby learns to better guess what the baby wants and gauges how well it is doing: the app claims to correctly pinpoint why a newborn cries 92 percent of the time—a high success rate that reportedly drops as the child grows older. A Spanish company offers a comparable product: its "Cry Translator" runs on smartphones (there is also a baby monitor) and takes only a few seconds to suggest what might be bugging the kid. Simultaneously, it advises its users on how to soothe their little one.

Of course, no algorithm will be able to substitute for good parental instincts. But cry analysis could support the child's caregivers—or possibly their doctors: in past decades researchers have found that infant squeals contain a treasure trove of information. Instead of focusing on the wants of the baby, as the app developers do, scientists have been trying to tease out information about potential health issues from baby cries. In infants' vocalizations, they have searched for signs of neurological damage and genetic defects. This diagnostic approach has an obvious advantage: the toddler might be spared more uncomfortable or even dangerous examinations.

French pediatrician Jérôme Lejeune pioneered this research in the 1960s. He discovered that some babies' high-pitched screams—almost catlike in sound—signal that these children are suffering from a genetic defect similar to Down syndrome. Le-

Janosch Deeg is a physicist and science journalist based in Heidelberg. His physics background, particularly in frequency analysis, helped him understand the technical details of the cry analysis.

IN BRIEF

Baby Code

- Before they can speak, babies signal their wants and needs with cries.
- Several brain regions help coordinate the vocalizations by sending signals to the larynx, vocal cords and chest.
- Scientists have found clues to neurological disease in the frequency spectrum of infant screams.

jeune aptly named the disease *cri du chat,* which translates as "cat cry." The eponymous shrill squeals are caused by a malformation of the infant's larynx. Affected children show various other symptoms, including growth defects, muscular dystrophy and a small, elongated head with a round face. To diagnose the disease, doctors always confirm their suspicions with a genetic test. Still, the distinct cries are a first, clear indication of the condition.

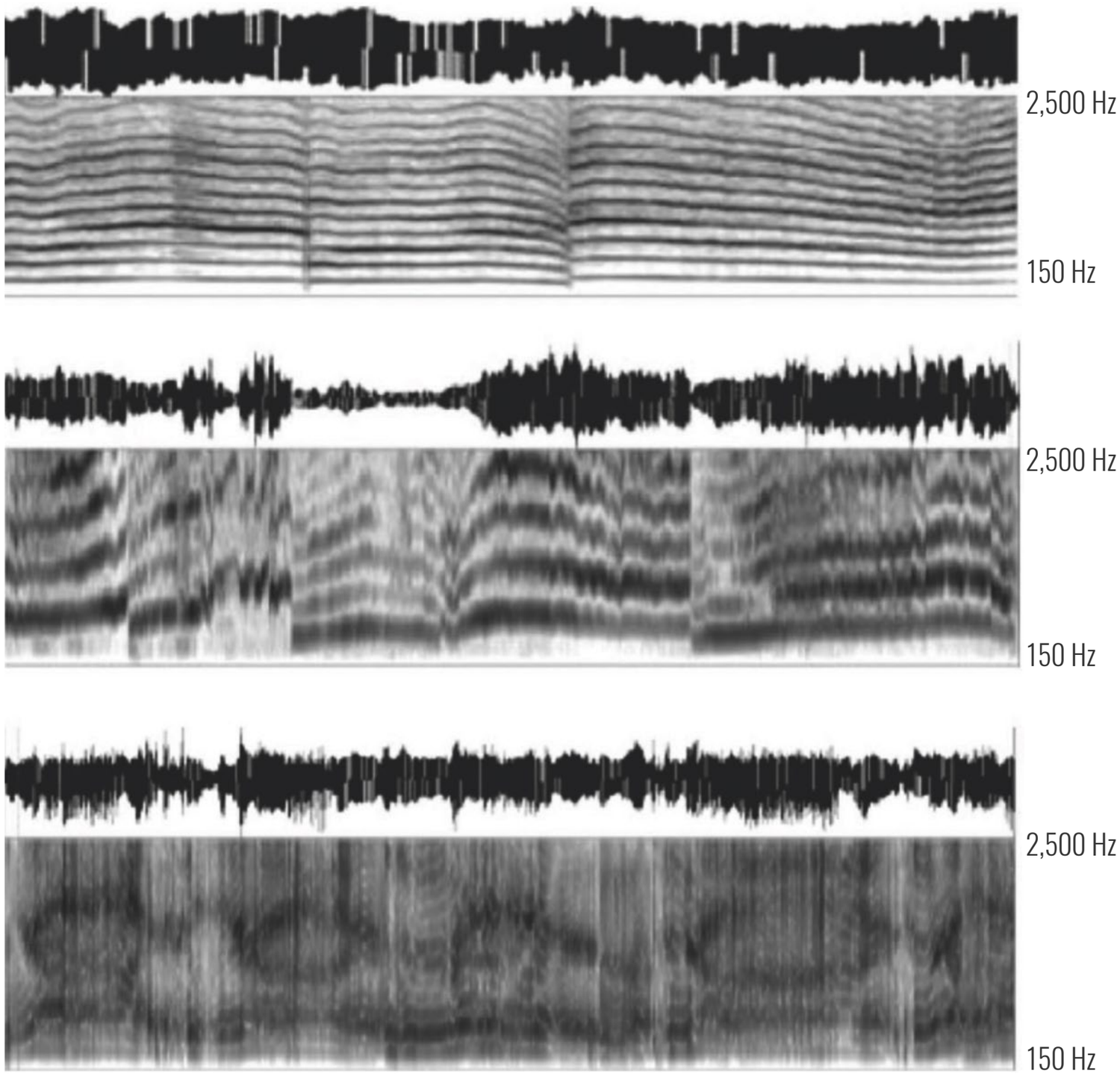
The larynx has a central role in almost all human sound production. Part of the breathing apparatus, it separates the throat from the windpipe. Together with the so-called vocal folds (also called vocal cords), it creates vocalization and speech. Any utterance starts here, with a tightening of the muscles around the vocal cords. When air is expelled from the lungs, the taut vocal cords begin to vibrate, which lets off a sound. Depending on the tautness of the vocal cords, the pitch rises—a cry of a healthy newborn produces 250 to 450 oscillations a second.

A child's scream is unique in many ways. Its basic pitch is determined by the interaction of the vocal cords with the larynx. Together they create a "dominant frequency," which forms the base of an individual's vocalizations. Yet a voice is not static—it can be modulated to some degree. Properties such as volume, rhythm and overlaid tones produce variation within the vocal spectrum. These features are created predominantly by areas below the larynx, including the diaphragm, lungs and chest. The upper vocal tract mostly takes on the fine-tuning: it amplifies some frequencies but leaves others unaltered or suppresses them. The complex interplay creates the entire spectrum of human vocalization.

The impulse to cry originates in the brain in the limbic system and hypothalamus. From here neuronal signals spread to other brain regions, such as the brain stem and the cerebellum, which coordinate the formation of sounds. Signals are then sent to the muscles of the vocal cord, larynx, chest and stomach via a highway of nerves that runs through the spinal cord. The different components work like an orchestra: all parts contribute to the final makeup of the vocalization. If one or several of the contributors botch their part, the tune is off. Certain kinds of brain damage interfere with this complex interplay, and in this way, they may alter a baby's cry.

Determining which parts are out of tune often needs more than an attentive listener. Scientists use technical aids that break a sound into its components and pick up on even the smallest abnormalities (irregularities). In 2013 doctors and engineers at Brown University announced they had developed a frequency analyzer that could screen an infant's voice recordings for 80 different acoustic properties. According to the researchers, each of them may hint at potential health problems.

Their analysis is a two-step process: Initially, the software cuts the recorded cry into 12.5-millisecond snippets and scans them for sound frequency, volume and voicing (indicating the degree of involvement of the vocal cords). In the second step, the researchers use the gathered insights to categorize longer sections of the recording into "continued vocalization," "silence" and "single scream." Finally, the software analyzes different characteristics such as pauses in-between the cries, average pitch and change in tonality over time. Stephen Sheinkopf, a pediatrician at the Women and Infants Hospital of Rhode Island and one of the scientists involved in the development of the tool, envisions that this



FROM 'ACOUSTIC MEASURES OF THE CRY CHARACTERISTICS OF HEALTHY NEWBORNS AND NEWBORNS WITH PATHOLOGIES,' BY YASMINA KHEDDACHE AND CHAKIB TADJ, IN *JOURNAL OF BIOMEDICAL SCIENCE AND ENGINEERING*, VOL. 6; AUGUST 2013

analysis could help diagnose autism at an early age. "It has long been known that [autistics] produce unusual sounds," he explains. Moreover, the spectrum of disorders that could manifest in babies' cries may be large. Trauma and brain damage, for example, are rare birth complications that are tricky to diagnose. "Cry analysis may enable doctors to identify children suffering from these conditions earlier," Sheinkopf believes. They could then monitor the infant carefully and respond quickly should sudden problems arise.

Infants' cries are like "a window to their brain," says Barry Lester, a psychiatrist at Brown and primary investigator of the acoustic analyzer study. He had started to investigate the hidden messages in babies'

TELLING PATTERNS

Spectrograms (visual representations of frequency spectrums) sometimes reveal health problems in an infant at first sight. The top pattern was recorded from a healthy newborn; the middle and the lower spectrograms were from a baby with microcephaly and one with oxygen deprivation, respectively.

squeals in the 1970s. At that time instruments were much less sophisticated than the tool he helped to develop in 2013, Lester asserts. Researchers still had to work with simple spectrograms—graphic representations of the spectrum of frequencies of the sounds. Technicians analyzed the graphs, a task that was mostly done by hand. Yet even with these limited means, several important discoveries were made: in the 1960s Vincent R. Fisichelli and Samuel Karelitz of the Long Island Jewish Medical Center deduced that specific irregularities in the frequency analysis hinted at brain damage in newborns. The cries of these infants were too high-pitched, too short and featured double tones. Moreover, the babies showed a delayed response after being exposed to pain triggers.

Years later a team led by child care expert Katarina Michelsson of the University of Helsinki found another such link in infants: unusually shrill sounds coupled with an irregular basal frequency point toward a higher risk of death by suffocation. She went on to uncover several other syndromes tied to changes in the screams. Among them were encephalitis, hydrocephalus and Krabbe's disease—a genetic defect that leads to progressive nerve damage and sometimes triggers bouts of screaming in affected children.

Sudden infant death syndrome (SIDS) has no known cause and displays no early symptoms. A group of researchers led by Lester and Michael J. Corwin of Boston University decided to screen babies' cries for warning signs. In a large study in 1995, the team recorded cries of 20,000 healthy newborns and analyzed them for abnormalities using a computer-based method. In the course of the investigation, 12 infants died from SIDS. In their cries the researchers discovered certain traits that point toward a constriction of the upper vocal tract and a perturbation of the neuronal control of this area. Many children who did not die from SIDS, however, showed the same characteristic pattern. Thus, although the method identified a risk group, it was not suitable for routine medical screening, because there were too many false positives.

In the 1970s researchers became interested in whether drug consumption during pregnancy could affect the offspring's screams. A team led by George Blinick, at the time at the Mount Sinai School of Medicine, had discovered that children from opioid-addicted mothers wailed at higher

Mother Tongue Affects the Sound of Cries

Babies do not only cry for attention—the wails also help them to learn how to talk. While they are screaming, they practice melodies that will later help them speak. A team led by biologist Kathleen Wermke of the University of Würzburg discovered that French newborns wailed differently than their German counterparts. While the French babies often produced ascending sound sequences, the Germans did the opposite.

The scientists believe this is because of the differing patterns of emphasis in the two languages. The fetus already notices the speech melody in the womb and practices to reproduce it once born. The older the babies, the more they learn to vary and combine the building blocks that make up the language. At some point, this allows them to speak their first word and then sentence—and ultimately to become fluent in the language.

pitches. Lester became interested in that observation two decades later and set out to investigate this relation in greater detail. The babies he and his team studied in the following years had been exposed to drugs such as marijuana, alcohol, opiates and cocaine in their mother's womb. The scientists observed various unnatural scream patterns, such as extremely high-pitched cries and an excessive amount of short interruptions. That, in combination with other irregularities, clearly points to problems in the control of breathing and the vocal tract in these infants—changes that are probably caused by neuronal damage and developmental defects of their nervous system.

Teasing out auditory effects of maternal drug consumption during pregnancy is still a hot topic in the cry analysis field. The technical means to study these phenomena have improved greatly since the 1970s. In 2014, using modern voice recording and analyzing equipment, a team led by Philip S. Zeskind of the University of South Carolina found evidence for differential effects in infants whose mothers had consumed cocaine while pregnant. The main determining factor was gender: affected boys screamed at a higher pitch and their vocalizations sounded unnaturally coarse. Girls, on the other hand, cried at a lower volume with fewer repeats and longer pauses.

Stressful stimuli do not affect males and females in the same way—that much was known previously. Scientists had also already suspected that contact with cocaine in the womb could have sex-specific effects on infants. They had found that girls displayed reduced responsiveness to their environment, whereas boys appeared chronically overstimulated. Only recently have Sheinkopf and Lester uncovered a factor that may help explain a differential response: in an article in June 2016 the researchers reported that the screaming tone depends on the expression of a gene that contributes to shaping the body's stress response. They thereby observed a link between the sound of the wails and the effects of the drug withdrawal on the unborn child.

Over the years a long list of scream traits has been analyzed. Aside from obvious characteristics such as duration, volume and interruptions, scientists have looked at tonic keynote, superimposed tones, variability and dysphonia (which includes hoarseness and roughness of the voice, for example). For every feature, they investigated how it can deviate from the norm. A single disruption—for example, a fault in the regulation of the breathing apparatus or of the vocal cords—often causes an unusual pattern to emerge. These observations do not yet suffice to diagnose disease reliably enough. In many cases, a variety of health problems can affect the screams in a similar way. Conversely, different irregularities in the cries are sometimes caused by the same dysfunction. Doctors can detect traits that are out of the norm, but further examinations are necessary to make conclusive diagnoses.

Clinics are currently not using the method because of these limitations. Sheinkopf believes that more validation studies could persuade them to embrace the technique. "Cry analysis might become an independent diagnostic tool or part of a package that aims to estimate risk for diseases such as autism," he hopes. Until then, it may be best to trust in parental instincts and listen for hidden messages in your infant's cries. If your inherent translator fails, there is always trial and error: feed, cuddle, sing. An app would not recommend anything more sophisticated either. M

Schizophrenia's Unyielding Mysteries

Gene studies were supposed to reveal the disorder's roots. That didn't happen. Now scientists are broadening the search

By Michael Balter

PHOTOGRAPHS BY ETHAN HILL; GROOMING BY AKANE ANJAWI *SUSAN PRICE, INC.*

Last year, when researchers in Cambridge, Mass., announced that they had found a gene strongly linked to a higher risk of schizophrenia, the news media reacted with over-zealous enthusiasm. A "landmark study," declared both the *New York Times* and the *Washington Post*. "Ground-breaking," trumpeted CNN. Even the *Economist* dropped its normal reserve: "Genetics throws open a window on a perplexing disorder."

The hype was somewhat understandable. Historically, schizophrenia research has left a trail of disappointment. The biological basis of the illness, one of the most puzzling and complex mental disorders, has long been an enigma. The toll, however, has always been clear. In the U.S. alone, estimates place the total cost of caring for patients at more than $60 billion a year, a figure that includes both direct health care costs and indirect economic losses from unemployment and early death. Any breakthrough in understanding the causes of the illness would be a major medical advance.

Since the advent of large-scale genetic studies just more than a decade ago, hopes have risen that new insights and therapies were on the way. They are much needed. Existing antipsychotic drugs dampen only the most overt symptoms, such as delusions and hallucinations. They often cause serious side effects and do little or nothing for chronic symptoms such as social withdrawal and cognitive deficits.

But genetic studies have yet to deliver on this promise. Gargantuan gene studies for schizophrenia, as well as depression and obsessive-compulsive and bipolar disorders, have driven home the message that most likely no single gene will lead to new treatments. The study behind last year's exuberant headlines was no exception. If nothing else, though, that research provides an inside look at the immense difficulties in understanding the mental processes that veer off course in schizophrenia.

The 1 Percent

Scientists who study psychiatric disorders had solid reasons to think that genetic clues might help overcome the field's stagnation.

Michael Balter is a freelance journalist, whose articles have appeared in *Audubon*, *National Geographic* and *Science*, among other publications.

IN BRIEF

Gene Hunt

- Massive genetic studies, it was hoped, would help discover the underlying causes of schizophrenia, a pyschiatric disorder that produces a toll in the U.S. of $60 billion annually for patient care. Research toward achieving this goal began about 10 years ago.
- The findings have not lived up to their original expectations. Studies have made clear that no single gene will lead to new treatments and that the tangled genetic landscape of schizophrenia is at best a series of faint hints of what causes the illness.
- The way forward will require that the field act on a mix of clues that suggest that early-life influences—such as childhood trauma and prenatal factors—exacerbate the impact of genes in elevating the risk of a diagnosis.

Decades of family and twin research suggest a strong genetic component to schizophrenia risk—one underlined by the steady rate at which the disorder occurs. Its prevalence is estimated to be about 1 percent throughout the world, notwithstanding vast environmental and socioeconomic differences across societies. Geneticists also knew that the hunt would not be straightforward. Individual genes powerful enough to generate a high risk of schizophrenia were likely to be very rare in the overall population and thus relevant to only a small percentage of schizophrenia cases. More common genes, on the other hand, would have much smaller effects in triggering schizophrenia and thus be much harder to detect. To find them would require greater statistical power, which would mean working with big sample sizes—tens of thousands of cases and control subjects. Acknowledging the challenges at hand, scientists in 2007 launched the Psychiatric Genomics Consortium (PGC) to study schizophrenia and other mental disorders. At present, the PGC has more than 800 collaborators from 38 countries and samples from more than 900,000 subjects.

Michael O'Donovan, a psychiatric geneticist at Cardiff University in Wales and chair of the PGC's schizophrenia working group, says a global approach was essential to assembling the "truly enormous sample sizes" needed to do the job in what is known as a genome-wide association study (GWAS). A big splash came in July 2014, when the group reported a GWAS involving about 37,000 schizophrenia cases and 113,000 control subjects. The study identified 108 genes (genetic regions) linked to schizophrenia, including a number that code for brain-signaling systems, the main targets for current antipsychotic drugs. These correlations were a sign that researchers might be on the right track.

The genetic region that showed the strongest link to schizophrenia codes for proteins of the major histocompatibility complex (MHC), which is intimately involved in recognizing molecules alien to the body and alerting the immune system. That discovery led Steven McCarroll, a geneticist at the Broad Institute of Harvard University and the Massachusetts Institute of Technology, to think that the MHC region might be a good target for additional study. When McCarroll's team probed further, it turned up a variant of *C4*, an MHC gene, that elevated schizophrenia risk from about 1 to 1.27 percent in the populations studied.

Although that is a relatively small increase, the researchers suggested in their report in *Nature* that it could hint at how some cases of schizophrenia arise. The *C4* results were important for other reasons as well. Variations in human *C4* consist not only of differences in the gene's DNA sequence but also of disparities in its length and how many copies of that gene an individual has.

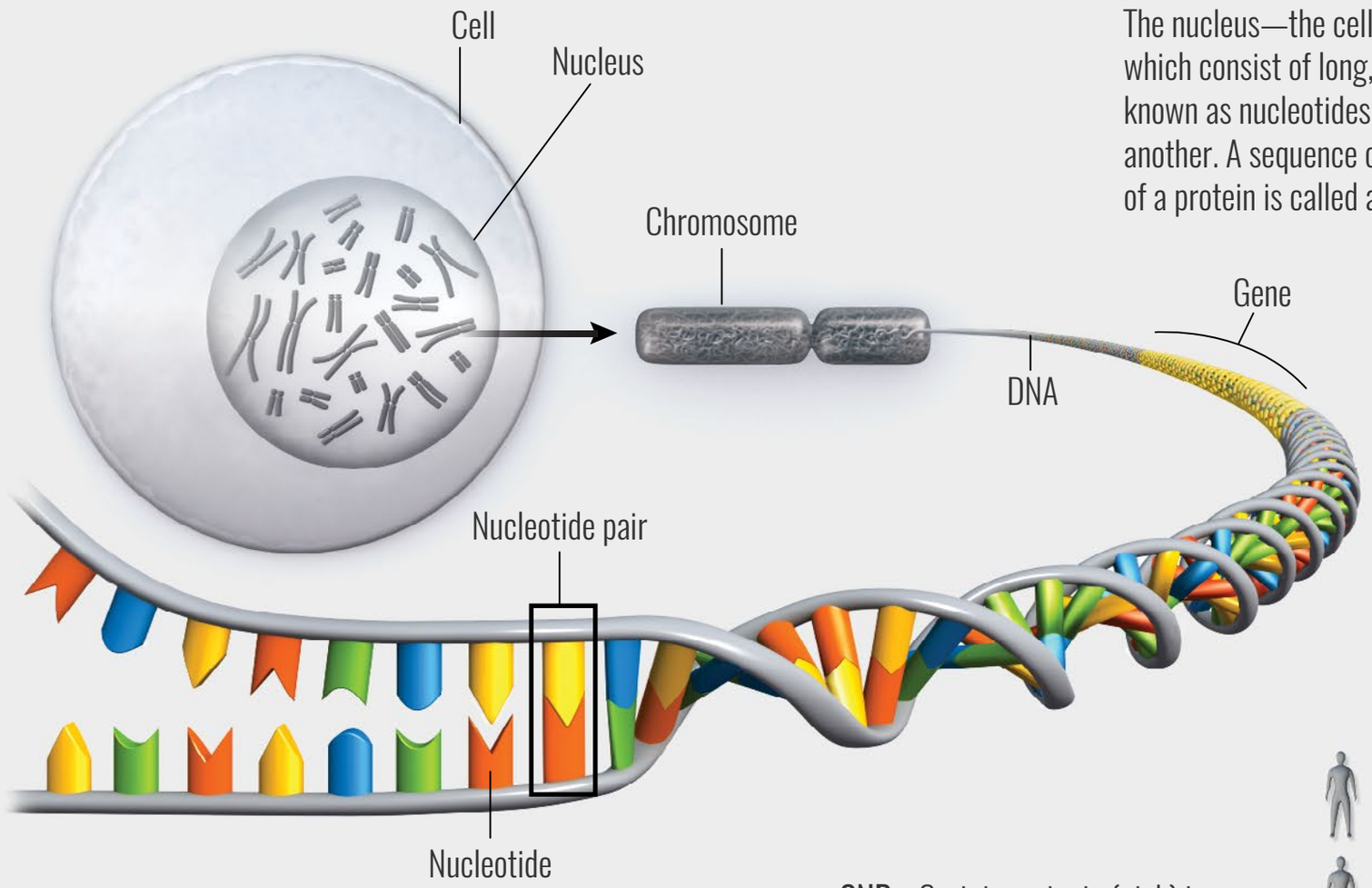
From previous studies, scientists suspected that relatively rare copy number variations (CNVs) played important roles in schizophrenia—and they continue to debate whether key schizophrenia genes are likely to be uncommon variants that raise risk dramatically or common versions that increase risk only slightly. The new study provided strong confirmation of CNVs' tie to schizophrenia. And when the team compared the brains of both living and deceased schizophrenia patients with those of control subjects, it found that markedly more of the *C4* protein was produced in the patients' brains, which was associated with the presence of additional copies of the gene.

Research Dragnet Falls Short

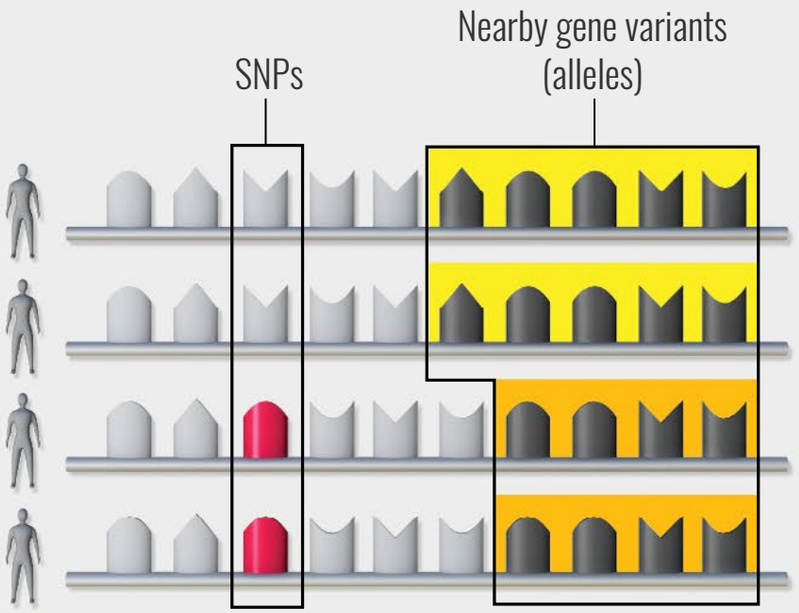
When the first rough draft of the Human Genome Project appeared in 2000, the research community thought it might herald an era of personalized medicine that would bring new therapies for a range of diseases, including psychiatric illnesses, such as schizophrenia. Large-scale studies that have identified variations in the makeup of genes that elevate the risk of schizophrenia have not yet provided solid leads for new treatments.

BASICS

The nucleus—the cell's command center—houses 23 pairs of chromosomes, which consist of long, threadlike stretches of DNA. Building blocks of DNA, known as nucleotides, carry varying genetic code "letters" that pair up with one another. A sequence of nucleotides that provides the instructions for the making of a protein is called a gene, variants of which are called alleles.



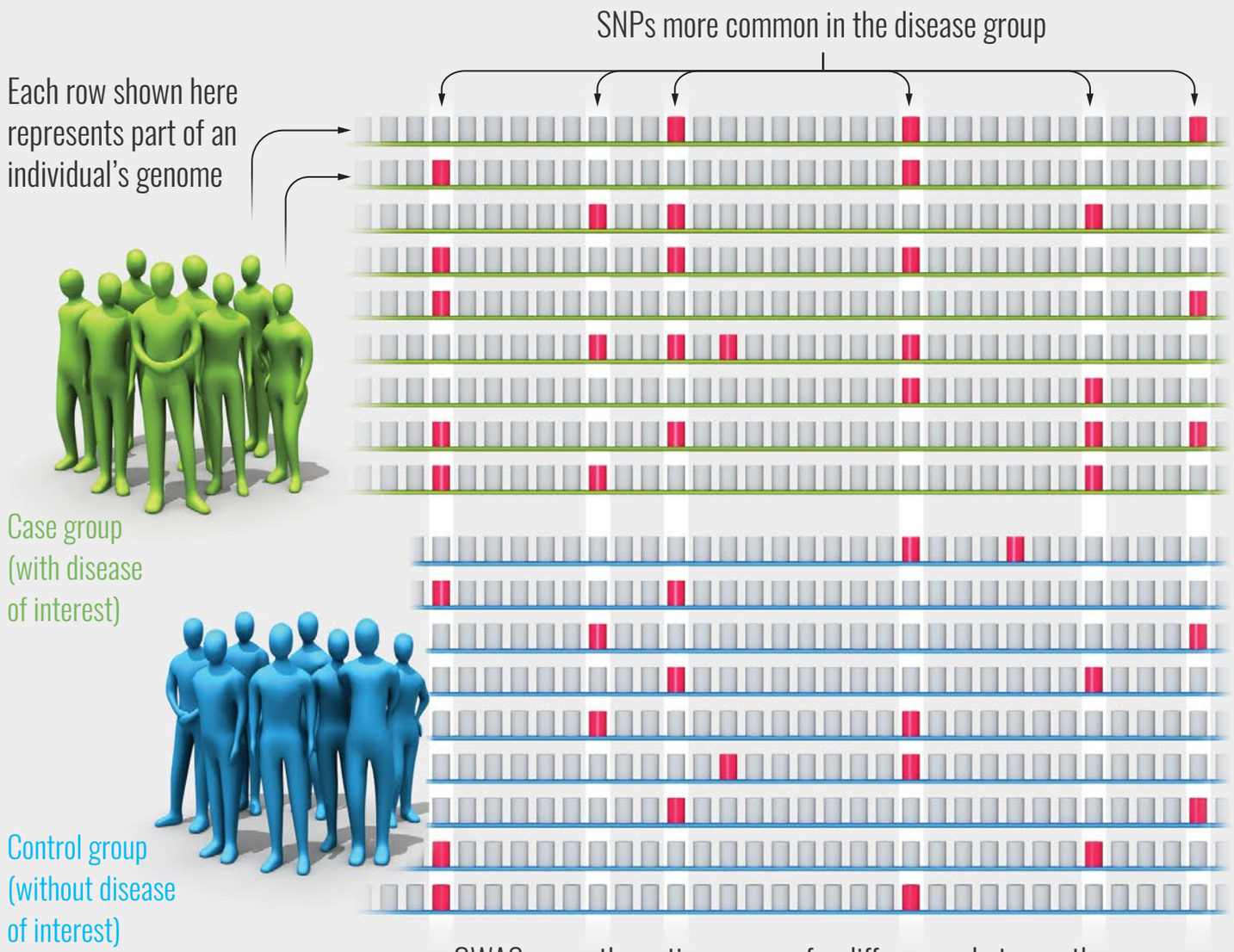
SNPs: Certain variants (pink) in a sequence of DNA—single-nucleotide polymorphisms, or SNPs—contribute to disease risk or serve as signposts that indicate the presence of nearby alleles associated with an illness.



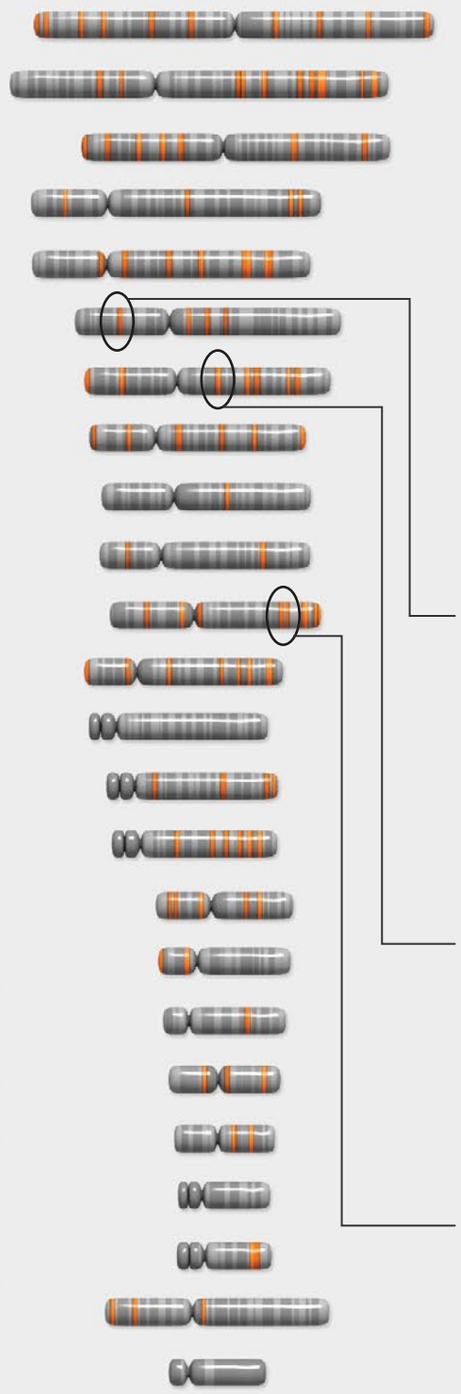
CREDIT: EMILY COOPER; SOURCE: "BIOLOGICAL INSIGHTS FROM 108 SCHIZOPHRENIA-ASSOCIATED GENETIC LOCI," BY SCHIZOPHRENIA WORKING GROUP OF THE PSYCHIATRIC GENOMICS CONSORTIUM, IN *NATURE*, VOL. 511; JULY 24, 2014 (*108 SNP DETAILS*)

HOW GENOME-WIDE ASSOCIATION STUDIES WORK

Researchers mill through hundreds or thousands of SNPS or other genetic variants in the DNA of thousands of individuals to look for genetic variants that turn up more frequently in people with a certain illness. Such a genome-wide association study (GWAS) investigates complex diseases in which many genetic variants may contribute to a person's risk. (Other genetic conditions may be caused by a mutation in a single gene.)



GWAS scans the entire genome for differences between the disease and control groups. It employs sophisticated statistical analyses to pick up even small increases in the number of specific genetic variants that might contribute to disease risk.



SCHIZOPHRENIA GWAS

A massive GWAS analysis published in 2014 identified 108 SNPs and other variants weakly correlated with schizophrenia from a study population of 37,000 schizophrenia cases and 113,000 controls. No single culprit emerged. But some of the variants helped to code proteins related to brain-signaling neurotransmitters; others were involved with the immune system. Here are three genes that stood out in this study and one in 2016.

C4: Helps with pruning synapses that are no longer needed. If this process is overactive, the immune-related protein may trim too many of these neural junctions, perhaps contributing to the dysfunction of schizophrenia.

GRM3: Involved with neural signaling by the neurotransmitter glutamate, the gene has several SNPs associated with schizophrenia. It has also been tied to other psychiatric disorders.

DRD2: Interacts with dopamine, a neurotransmitter implicated in schizophrenia. As a dopamine receptor, *DRD2* is the primary target of antipsychotic drugs.

CREDIT: EMILY COOPER; SOURCE: "BIOLOGICAL INSIGHTS FROM 108 SCHIZOPHRENIA-ASSOCIATED GENETIC LOCI," BY SCHIZOPHRENIA WORKING GROUP OF THE PSYCHIATRIC GENOMICS CONSORTIUM, IN *NATURE*, VOL. 511; JULY 24, 2014 (*108 SNP DETAILS*)

To look more closely at what *C4* does at the molecular level, the researchers turned to mouse brains. Beth Stevens of the Broad Institute, who spearheaded this part of the study, found that the protein assisted in brain development by "pruning" neural connections, called synapses, when they are no longer needed. Synaptic pruning is a normal part of brain maturation. But if this process is overactive and pares back too many synapses, it could perhaps elucidate some of the features of schizophrenia. It might explain why affected patients tend to have thinner cerebral cortexes and fewer synapses. And schizophrenia, along with other forms of psychosis, is usually first diagnosed in people in their late teens or early adulthood, when brain maturation reaches its final stages.

For some scientists, the finding was a vindication for GWAS as a relatively new way to hunt down disease-associated genes. GWAS has triggered an "amazingly positive and unprecedented explosion of new knowledge" about mental disorders, says Patrick Sullivan, a psychiatric geneticist at the University of North Carolina at Chapel Hill School of Medicine. As for the *C4* study, David Goldstein, director of Columbia University's Institute for Genomic Medicine—who has long been a skeptic of GWAS's potential—says that by pointing the way to a possible biological pathway for schizophrenia, the new finding represents "the first time we have gotten what we wanted out of a GWAS." Others, including some leading geneticists, are less certain, however. "GWAS will have no impact on resolving the biology of schizophrenia," says Mary-Claire King of the University of Washington, who in 1990 identified *BRCA1* as a major risk gene for breast cancer.

In scientific parlance, most cases of schizophrenia appear to be highly "polygenic"—hundreds or perhaps thousands of genes are involved. "GWAS shows that schizophrenia is so highly, radically polygenic that there may well be nothing to find, just a general unspecifiable genetic background," says Eric Turkheimer, a behavioral geneticist at the University of Virginia.

Indeed, it might be argued that one of GWAS's most important contributions—and the *C4* study was no exception—has been to disabuse researchers of simplistic notions about psychiatric genetics. The new findings so far have dashed hopes that schizophrenia can be pinned on just one or even a few genetic mutations. The skepticism stems from the realization that each of the 108 genetic locations linked to schizophrenia so far confers only a tiny risk for the disorder. And the few genes that confer a high risk—in the case of copy number variants and other rare mutations—account for only a small percentage of schizophrenia cases. That makes it less likely that the new findings will lead to therapies anytime soon. It also poses obstacles for neuroscientists and psychiatrists who hoped to find genetic clues for the underlying roots of the disorder. "It would have been way better if there were one single gene," says Kenneth Kendler, a psychiatric researcher at the Virginia Commonwealth University's School of Medicine. "Then all of our research could have gone into that area."

In the case of *C4*, a recognition of these limitations has led to questions about just how relevant the gene will be to understanding schizophrenia or developing new therapies. Whereas about 27 percent of the nearly 29,000 schizophrenia patients in the study had the highest-risk *C4* variant, roughly 22 percent of the 36,000 healthy control subjects also carry it, according to

McCarroll. "Even if the *C4* story is right, it accounts for only a trivial amount of schizophrenia," says Kenneth Weiss, an evolutionary geneticist at Pennsylvania State University. "How useful that will be is debatable." And the study does not prove a direct relation between synaptic pruning and schizophrenia, McCarroll and others concede. Its importance seems to lie more in its potential to help pinpoint what kinds of biological pathways might be involved.

Still other problems beset GWAS. To procure huge samples, geneticists usually distinguish between cases and controls depending on whether a person has received a formal schizophrenia diagnosis or not. But the criteria are very broad. In the U.S., the diagnostic rules are dictated by the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, whereas many psychiatrists in other countries rely on the World Health Organization's *International Classification of Diseases*. In the criteria set out in both volumes, patients can have markedly different symptoms, ranging from delusions to hallucinations to cognitive defects, and still be diagnosed with a case of schizophrenia.

Hannelore Ehrenreich, a neuroscientist at the Max Planck Institute of Experimental Medicine in Göttingen, Germany, describes schizophrenia as "an umbrella diagnosis" rather than a distinct disease: "We are focusing on people who are on the extreme end of human experience, who are part of a continuum and not a separate category." William Carpenter, a psychiatrist at the University of Maryland School of Medicine and editor in chief of the flagship journal *Schizophrenia Bulletin*, does not go that far, but he acknowledges that schizophrenia is a group of disorders or symptoms and not a distinct disease. "That makes it a weak target for gene discovery," he says.

Goldstein, who thinks the *C4* findings "are the best case we've got" for understanding how a schizophrenia risk gene might exert its effects, still calls for researchers to express "a whole lot more humility" about GWAS results. "People working in the schizophrenia genetics field have greatly overinterpreted their results."

Some of the strongest skepticism about the search for schizophrenia genes comes from psychiatrists, patient advocates and former patients themselves. The GWAS approach focuses on finding new drugs to lessen symptoms of the disorder. But patients often look askance at this goal. "This obsession with symptom reduction does not entirely correspond with the viewpoint of the patients," says Jim van Os, a psychiatrist at the Maastricht University Medical Center in the Netherlands. Rather, van Os says, patients want to be able to live productive lives and function in society—and doing so does not necessarily correspond with being more medicated.

Van Os and a growing number of patient advocates argue that the term "schizophrenia" itself is part of the problem because it stigmatizes and dehumanizes patients without adequately describing what is wrong with them. Jim Geekie, a clinical psychologist who works at a National Health Service inpatient unit just outside London, says that "knowing somebody's diagnosis tells me next to nothing about them."

Indeed, a number of countries and regions in Asia, including Japan, South Korea, Hong Kong and Singapore, have eliminated the classification altogether. The Japanese term "mind-split disease," used to describe a person with schizophrenia, has been changed to "integration disorder," and a

similar term in Korean has been changed to "attunement disorder."

For many researchers and advocates, the main problem with the nomenclature—and with the gene search itself—is the lingering implication that patients are suffering from a form of brain disease. "If there are genetic variations that mean some people are prone to having these experiences, then we need to make sure people's environments don't switch these things on," says Jacqui Dillon, chair of the U.K.'s Hearing Voices Network. Dillon, who was told as a young woman that she had schizophrenia and still hears voices today, adds that understanding schizophrenia genetics "doesn't change what we need to do to keep people from going mad."

A Deep Flaw

Some researchers insist that the search for genes is misguided because it largely ignores the environmental context, as well as the personal and family circumstances, that contributes to schizophrenia risk. "The whole enterprise is deeply flawed," says University of Liverpool psychologist Richard Bentall. This view is especially strong among clinicians, such as Bentall, who directly treat schizophrenia patients. They argue for increased funding for pragmatic, nonbiological approaches, ranging from family therapy to cognitive-behavioral therapy (CBT).

At times, questions also arise about the fundamental idea, derived largely from family and twin studies, that schizophrenia has a high "heritability." This term is often assumed, even by many scientists, to mean that genetic factors play a major role. Yet the concept of heritability is complex and not a direct measure of how "genetic" a particular trait—such as a formal schizophrenia diagnosis—actually is [*see "Heritability: Missing or Just Hiding?"*].

In fact, environmental and social factors, some researchers insist, confer a greater schizophrenia risk than most genes identified so far. Epidemiological studies have shown that risk factors range from living in an urban environment or being an immigrant to experiencing poverty and emotional and sexual abuse.

Just how such factors contribute to schizophrenia risk is not well understood, aside from speculations that they are sources of emotional stress. Recently, for example, an Israeli team found that Holocaust survivors suffered higher rates of schizophrenia. Another group found increased

risk among people who had lived through the violent "Troubles" in Northern Ireland.

There is growing evidence that progress can be made only if researchers consider a spectrum of risk factors. Whereas genetics may make some people more vulnerable to mental disorders, influences from family or a social circle may push a susceptible individual across a threshold that results in a first psychotic episode. The key task is to figure out how genetic and environmental factors interact to produce schizophrenia.

Even diehard gene jockeys admit that environmental influences must be playing some kind of role. "Genes are not destiny," McCarroll agrees. He points out that when one member of a pair of identical twins is diagnosed with schizophrenia, the other twin is affected by the disorder only about half of the time—a clear indication that nongenetic factors must be important.

Environmental Roots

Frustrations in the hunt for schizophrenia genes have forced the field to reassess how to move forward. Genetics is still considered important to understanding the biological underpinnings of the disorder and coming up with new drugs. But most researchers and clinicians now agree that a broader strategy that supplements genomic approaches is needed, one that builds on expertise gained from experts in sociology, psychotherapy and even prenatal health.

Over the past several years psychologists, psychiatrists, epidemiologists and social workers have accumulated a deeper understanding of the environmental and social factors underlying the disorder. Many new studies are now focusing on "childhood adversity," an umbrella term that includes sexual, physical and emotional abuse, neglect, bullying, and the loss of one or more parents.

One of the most widely cited of these studies, a meta-analysis by van Os and his colleagues, published in 2012 in *Schizophrenia Bulletin*, combined results from several studies to increase statistical power and found that patients suffering psychotic symptoms were nearly three times as likely to have been the victims of adversity, far greater than the risk of any gene identified so far in a GWAS. "We need a stronger focus on changing the environment so we can prevent schizophrenia," says Roar Fosse, a neuroscientist at the Vestre Viken Hospital Trust in Norway. "We need to give children better childhoods and better chances to avoid extreme stress."

And in a 2014 paper in the *Lancet*, Ehrenreich and her colleagues demonstrated how studies that combine genetic and environmental data can provide new insights. The team reported on 750 male schizophrenia patients in Germany for whom—unusually—both GWAS and detailed environmental and social risk data were available. The team looked at the age of schizophrenia onset in these patients, a key indicator of how well they are likely to do over the long run: the earlier the age of onset, the worse the eventual outcome. It found that environmental factors, including early brain damage, childhood trauma, living in an urban environment, coming from an immigrant family, and especially cannabis use, were significantly associated with earlier onset. The average age of onset was nearly 10 years earlier for patients who had four or more environmental risk factors than for those who had none. On the other hand, so-called polygenic risk scores calculated from the GWAS data had no detectable effect on age of onset.

Ehrenreich does not interpret these results to mean that genes are irrelevant. It is

more likely, she says, that "the genetic factors are so different from one individual to the next that each person has a different reason for having the disorder." Other researchers, meanwhile, are looking at how environmental stresses, at home or school or through exposure to certain chemicals, might turn genes off and on—a pursuit known as epigenetics.

Ehrenreich and others urge GWAS researchers to begin incorporating environmental data into their studies whenever possible so they can derive a statistical model of how genes and environment interact to make people sick. "It is a shame that researchers neglect assessing environmental information in some of the most expensive and technologically advanced genetic studies," says Rudolf Uher, a psychiatric researcher at Dalhousie University in Nova Scotia.

Unfortunately, combining epidemiology with genetics may be a tall order. "The cost of gathering environmental data is enormous, and there is considerable disagreement about how to define these environmental variables," Cardiff's O'Donovan comments. Even so, in 2010 the European Union funded a five-year pilot program to do just that, led by O'Donovan, van Os and others—and researchers have now begun analyzing the data generated.

The big question, of course, is whether the search for genes, even in the context of environmental influences, will eventually lead to new therapies. Most scientists agree that it will take many more years for this research to pay off in new drugs or other interventions. Genetics "has provided the first hard biological leads in understanding schizophrenia," says Peter Visscher, a geneticist at the University of Queensland in Brisbane, Australia. "It is too early to say whether these discoveries will lead to new therapies, but there is no reason why they could not." Psychiatric researcher John McGrath, also at Queensland, agrees: "The science is hard, and the brain is hard to understand. But there is no need to throw our hands up in despair."

Meanwhile, in parallel with the genetic studies, schizophrenia researchers are pursuing numerous other lines of inquiry. They have begun looking for biomarkers—telltale molecules in blood or brain anomalies from neuroimaging that might help them identify people at high risk for the disorder. This could lead to earlier treatment, which numerous studies demonstrate can lead to a better long-term prognosis. Prompted by studies suggesting that the children of women who come down with infectious diseases during pregnancy might be at higher risk for schizophrenia—possibly because of immune responses harmful to the brain of the fetus—other teams are testing anti-inflammatory compounds to see if they might reduce symptoms.

A number of recent clinical trials, meanwhile, suggest that psychosocial therapies, especially CBT, can help lessen both symptoms and suffering in schizophrenia patients. While this research is controversial and the effects are only modest so far, advocates of such approaches are gaining traction in both Europe and the U.S. In the U.K., for example, CBT is now recommended by government health authorities for all first-episode cases of psychosis. "The imbalance in funding between genetic and pharmacological research and psychosocial research needs to be addressed and corrected," says Brian Koehler, a neuroscientist at New York University who also treats schizophrenia patients in private practice. The intricacies of schizophrenia mean that comprehensive new treatments

Heritability: Missing or Just Hiding?

A concept that seems obvious is not

Researchers have been looking for schizophrenia-related genes for at least 50 years. What makes them think they will find them? The rationale is spelled out in the introduction to nearly every scientific paper on schizophrenia genetics: The disorder has a high heritability. This term is often interpreted as a measure of the relative role played by genes. Heritability is usually expressed as a percentage between 0 and 100 percent.

Scientists have estimated the heritability of schizophrenia using several approaches, including studies of twins. Most estimates hover around 80 percent. Many researchers argue that heritability estimates for schizophrenia can be very misleading, however. They question key suppositions, including the so-called equal environment assumption (EEA), which considers both identical and fraternal twins to be subject to the same environmental influences.

"These basic assumptions are wrong," says Roar Fosse, a neuroscientist at the Vestre Viken Hospital Trust in Norway, who led a recent critical assessment of the EEA. But twin researchers have mounted a vigorous defense of the approach. "I don't think it's likely that current heritability numbers are substantially overestimated," says Kenneth Kendler, a psychiatrist at the Virginia Commonwealth University's School of Medicine.

Some researchers have an even more profound critique of heritability. They argue that the technical calculations of the term do not account for the relative role of genes and environment. Heritability, rather, measures only how much the variation of a trait in a particular population—whether height, IQ or being diagnosed with schizophrenia—reflects genetic differences in that group.

As an example of how misleading heritability estimates can be, Eric Turkheimer, a geneticist at the University of Virginia, points to the human trait of having two arms. Nearly everyone in a given population has two of them, and there is normally no difference in the number of arms between identical twins—who share nearly 100 percent of their DNA sequence—and fraternal twins, who are assumed to share 50 percent of their genes on average. Thus, when heritability for arm number is calculated using standard heritability equations, it comes out to 0. And yet we know that having two arms is almost entirely genetically determined.

Figuring out what heritability for schizophrenia actually means is key, researchers say, because even the most high-powered genetic studies have identified only about a third of the predicted genetic component. Will this so-called missing heritability eventually show up in more sophisticated studies—or will it turn out that genes are not playing as big a role as heritability estimates have long predicted? The jury is still out. *—M.B.*

are still speculative. Researchers hope that one day brain imaging or other diagnostic tests may help spot a youngster at risk either before or during adolescence. If so, new medications and psychological counseling may be able to delay or prevent a first psychotic break. To achieve that goal, biologists and social scientists must continue to merge their expertise to piece together a composite profile of one of the most complex of all psychiatric illnesses. M

MORE TO EXPLORE

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FROM OUR ARCHIVES

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Lonely but Never Alone

Space travel: How does the brain react to the isolation encountered in outer space?

By Anna von Hopffgarten

ESA, IPEV, PNRA AND A. SALAM

Neuroscientist Stefan Schneider of the German Sport University Cologne looks for answers in a research station in Antarctica. Interview by Anna von Hopffgarten.

Hopffgarten: Humans are drawn ever farther into space, and flying to Mars may become possible in our lifetime. A trip to the Red Planet is now estimated to take about eight months each way, with a minimum stay of a year on the planet surface. What challenges would a mission like this pose for the psychological well-being of astronauts?

Schneider: A long spaceflight would impact a person in many ways. The astronauts would live in close quarters for a very long time—and a spacecraft really does not offer much room for retreat. That can be stressful. Another issue is the monotony: there is little variation in the daily routine of an astronaut, and the surroundings do not offer much diversion.

Anna von Hopffgarten is an editor at the magazine *Gehirn & Geist*.

Your latest study focuses on specific effects of isolation on the human brain and psyche. How did you investigate this?

We worked with volunteers among the staff of the Antarctic research station Concordia, whom we monitored for a period of eight months spanning the Antarctic winter. Of course, we would have loved to conduct experiments on a genuine space station—but for practical reasons, that was never really an option. Sending several people to outer space for months at a time would have been very expensive, and observing them in that environment is tricky from an experimenter's point of view. Therefore, we decided to set our study in a so-called analogous environment—in our case, the Concordia station. This building complex is secured on the top of a plateau, 1,000 miles from the South Pole. It looks like a giant soda can cut in half and is surrounded by only ice and snow. In many ways, the conditions our volunteers faced here are similar to those on a space station. Concordia is situated in one of the coldest places on earth: temperatures during our experiment averaged about –65 degrees Celsius (–85 degrees Fahrenheit). Under

COURTESY OF STEFAN SCHNEIDER

Stefan Schneider was born in Cologne in 1972. He obtained a Ph.D. in exercise science from the German Sport University Cologne, where he now acts as vice president. He also holds a doctorate in theology from the University of Bonn. Additionally, he holds an adjunct professorship at the University of the Sunshine Coast in Queensland, Australia. His academic interests revolve around the question of how the psyche and the brain react to extreme conditions, as well as the impact of sports on mental health. Anna von Hopffgarten, a biologist and science writer, interviewed him for *Gehirn & Geist*.

The Antarctic Concordia station is situated in one of the coldest places on earth, 320 miles (600 kilometers) from the nearest research facility. Minimum temperatures drop as low as –112 degrees Fahrenheit (–80 degrees Celsius) in winter, which makes supplying the living quarters with heat and water extremely challenging. The red containers in the picture are the station's power plant and its wastewater recycling plant.

VERA ABELN

these climatic conditions, no vehicle could reach the station. The station's inhabitants could go outside only for very short and only when weather permitted. They spent three of the eight months in the complete darkness of the polar night.

Who took part in your study?
Mostly they were scientists conducting research in Antarctica, like glaciologists and astronomers, but some of the station's support staff were among our volunteers, too—including an electrician, a cook and a medic. Of 14 Concordia crew members at the time, eight agreed to participate in our study.

What did their lives at the station look like?
The routine of a person was determined by their role—each had his or her own set of tasks. The scientists at the station ran experiments for their respective studies, the cook prepared the meals for the entire crew, and so on. The commander of the station regularly tried to get everyone together for a shared breakfast, so no one would break away from the group. Just like at a Boy Scouts camp, that idea sometimes worked and sometimes it did not. And once breakfast was over, everyone went their separate ways for the rest of the day to work their jobs.

How did you study the effects of isolation on the Concordia inhabitants?
Once every six weeks we asked our volunteers to fill in a questionnaire on their physical and psychological well-being. At this point we also measured their brain activity by EEG. Before the start of the study, we had prepared them to conduct the test procedure themselves because we could not physically be present and help them with the examination. In addition to the tests, four of our eight participants also took part in a sports program.

What kind of exercise did they do there?
The participants could use a small gym in the station, which is fitted with a treadmill and a few weights. Apart from that, the training consisted of exercises that use a person's own body weight, such as push-ups, pull-ups and rope skipping.

What are the results of your investigation?
The persistent isolation and the monotonous surroundings had a negative effect on the reported mood of the participants. This was, however, only the case with people who did not take part in the sports program. As early as six weeks after the start of the study, their well-being had already suffered. With increased psychological pressure, their motivation dropped, and they reported they felt less fit. Their levels stabilized at this lower than usual level.

What about people who were physically active?
Their mood did not suffer but instead remained constant for the whole test period.

How do you explain that?
We believe the positive impact of exercise is rooted in its effect on the prefrontal cortex. From previous studies, we know that this part of the brain—which is responsible for cognition and emotion—is less active after physical activity. Stress and discomfort, on the other hand, cause activity in this brain region to spike. We now believe that during sport, cortical activity shifts to other areas. That gives the prefrontal cortex the chance to "reset." You could imag-

Through this wood door is the huge ice tunnel where glaciologists keep their samples.

VERA ABELN

ine it as a computer chip on overdrive. Physical activity reroutes the entire brain circuit so that this area can recover. Sports therefore quite literally reboot the brain.

The study participants also monitored their brain activity at the Antarctic station. What were the results?

We measured the so-called alpha and beta waves with EEG. High levels of alpha activity indicate that the brain is in a relaxed state—as soon as we close our eyes, alpha waves start creeping up in an EEG. Beta waves, on the other hand, signify a state of awakeness. After six weeks at the station, both kinds of brain waves increased slightly in the nonsport group, whereas they dropped continuously in the sport group. At the end of the experiment, physically active persons displayed roughly 40 percent less alpha and beta activity than their less active co-workers.

How do you interpret these findings?

Normally, higher alpha activity would go hand in hand with increased relaxation—which would have implied that the inactive group was more relaxed than the sports group. Had this been the case, we would

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also have seen simultaneous decreases in beta activity. Because both alpha and beta waves are high in our nonsport group, we believe it is more likely that this represents a general increase in cortical activity in our volunteers. The extreme conditions these people had lived in—the cold and dark Antarctic winter, the lack of variation in scenery and routine, and the limited interaction with others—all that had left a mark on them. They were under psychological and physical stress, which may have caused their higher than usual cortical activity. Sports may have dampened this response in the second group. Still, caution is warranted when interpreting these findings: the comparison of alpha versus beta waves paints a picture that is too simplistic to make definite statements. In follow-up examinations, I would try to capture more detail with a much more thorough EEG analysis.

The Concordia station contains a laboratory where scientists perform their experiments. The EEG exams of Schneider's isolation study were also conducted in this room.

VERA ABELN

How does your Antarctica experiment differ from the Mars500 trial, where six volunteers simulated a 520-day flight to Mars?

In contrast to the Mars500 study, our volunteers were housed in a genuine research station where they had to fulfill an actual mission. Our glaciologists, for example, drilled holes into the ice to study its make-up. They had to face very real situations and problems, in many respects much like the ones that astronauts handle in longer space missions. One factor our experiment could not simulate, though, was a zero-gravity environment.

Locked into a tiny complex with 13 other people for several months—in that setting, it is hard to imagine loneliness would be a problem. Could your results come from the stress caused by the close proximity with this group?

No supplies can be delivered to the station during the eight-month winter period—all provisions for that time are stored in shipping containers.

In this environment, as in a real space mission, both states coexist: a sense of isolation or loneliness and the lack of personal space with little possibility for privacy. They are two sides of the same coin, and therefore we cannot differentiate them or treat them as separate factors in our experiments. One goes with the other.

Is it possible that the lack of personal space was an even bigger challenge than the isolation?

That surely is the case for some people—a lot depends on personality. You may remember the 2010 mining accident in Chile, where 33 people were stranded underground for 69 days. One of the survivors later said what kept him sane was the possibility of hiding away in the network of tunnels—by himself. So despite being cut off from the outside world, the miners still had some options to retreat and spend some time alone. Astronauts also repeat-

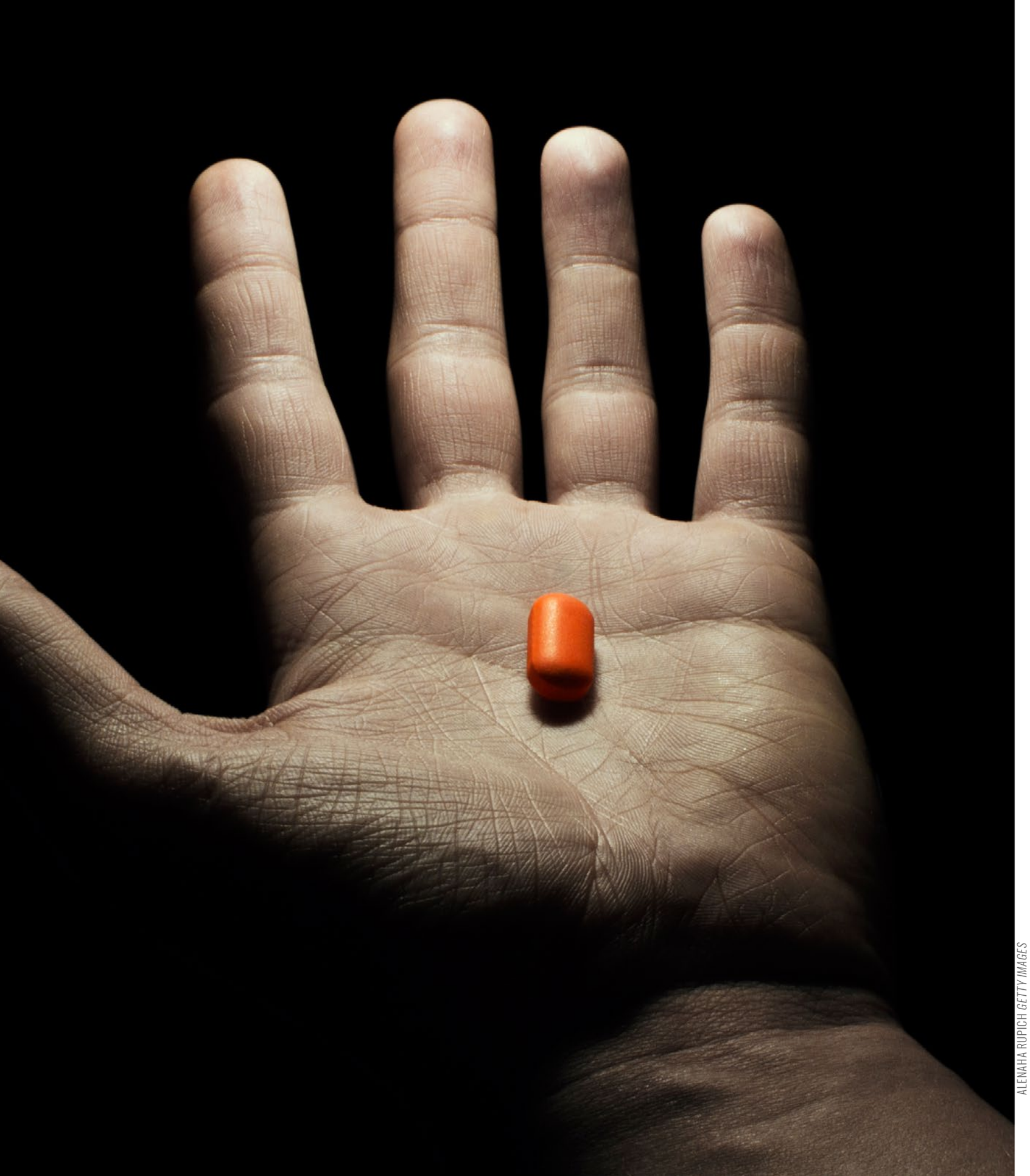
edly say that spending time in solitude is one of the things they miss most in space.

On your space mission, you usually cannot choose your fellow astronauts. Do you have any advice for how to best cope with interpersonal conflicts should they arise?
A crew will be put together with social criteria in mind. Before the mission starts, there are in-depth assessments of who gets along with whom and which people might antagonize one another. Additionally, astronauts receive psychological training, where they learn how to best deal with—or straight out avoid—conflicts. Still, it is important that everyone makes up their mind about how they can best relieve stress. Sport is one option to do so.

How about daily life: Would you recommend a stressed person to exercise more?
For some, that surely would be good. Elderly people in particular often slide into a vicious circle that begins with retirement. At that point a person may lose a majority of their social circle as well as their main reason to get up in the morning. Some react by withdrawing and staying at home most days—especially those who are not that fit later in life. That can gnaw away at their self-esteem. As a consequence, their physical health progressively recedes, and because of a lack of variation the brain is not fed enough sensory input—which, in turn, also leads to a decline in mental function. Those deficits draw up new hurdles that prevent a person from going outside and meeting new people. A regular workout may help counter that.

Those who may profit most from sports are lonely people. But some studies claim that, in general, they have trouble motivating themselves to exercise. Can you think of ways to solve this dilemma?
Deep down we all know that exercise is healthy. Still, that by itself does not seem to push everyone to exercise more. That is because part of our tendency to enjoy sports develops when we are young. If a child likes to move, they often come back to that in later life. So we should look for reference points from childhood: Which sports did I like as a child? Maybe I should give that another go! One thing that surely won't help is trying to convince someone to take up a specific activity without consideration for what the person may enjoy.

How do you cope with loneliness?
I actually enjoy every moment of solitude I get. That is why I like to jog in a forest, where I can find peace and quiet. M



ALENAHA RUPICH *GETTY IMAGES*

OPINION

How to Prevent Suicide with an Opioid

Fascinating study suggests treating "psychache"

By Anne Skomorowsky

The idea that suicide is caused by psychological pain may seem self-evident, but recognizing this fact was once a departure for psychiatry. Depression and other psychiatric disorders—which are often associated with suicide—are diagnoses, and diagnoses are the coin of psychiatry's realm. But psychological pain is an experience, one that may not be connected to any diagnosis.

The late psychologist Edwin Shneidman, who founded the Los Angeles Suicide Prevention Center in the 1950s, rejected the diagnosis-based medical model of suicidal behavior. He coined the phrase "psychological autopsy," a procedure he used most famously to establish Marilyn Monroe's death as a probable suicide. The "autopsy" consists of postmortem interviews with the family and friends of the deceased to establish his or her frame of mind and possible motives for suicide. The implication is that those who knew the victim intimately, not psychiatrists, are in the best position to understand the suicidal act.

Although a review of psychological autopsy studies showed that more than 90 percent of the suicides were associated with diagnosable mental disorders, Shneidman pointed out that no one has ever died of depression but rather of suicide. In an influential 1993 paper, "Suicide as Psychache," Shneidman proposed that "*Suicide is caused by psychache* ... hurt, anguish, soreness, aching psychological *pain* in the psyche, the mind." He objected to what he felt were simplistic categories when it came to understanding suicide: "If ... feeling guilty or depressed or having a bad conscience or an overwhelming unconscious rage makes one suicidal, it does so only because it is painful."

In the nearly 25 years since "Suicide as Psychache" was published, research into suicide has focused on destigmatization and the treatment of mental disorders, on neurochemistry and the role of serotonin and serotonin reuptake inhibitors, and on risk factors, such as ready access to guns. Now the concept of mental pain is making a comeback in response to recent neurobiological research, which suggests that pain is processed through the same structures and mechanisms in the brain regardless of whether it is physical or emotional.

Could mental pain be treated like physical pain, and would a reduction in suicidal thoughts follow? A surprising new study by Yoram Yovell of the University of Haifa in Israel and his colleagues addressed that question in a randomized, placebo-controlled trial of very low doses of an opioid, buprenorphine, in severely suicidal subjects.

The authors looked to the concept of "separation distress" to justify the trial of buprenorphine. All young animals, including humans, are distressed when separated from the attachment figures on whom their physical and emotional well-being depends. Very low doses of opioids have been known to ameliorate that distress since the 1970s. Yovell and his colleagues drew on attachment literature, which established that endogenous opioids—the ones that occur naturally in our brains—help us feel good when we are with loved ones. When we separate from loved ones, internal opioid levels drop, and we experience mental pain—the human version of separation distress.

Neurobiological studies have suggested that separation distress overlaps with pain

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circuitry in the brain in a general "neural alarm system" when an animal, or a person, is under threat. A trial of opioid painkillers, which might quiet that neural alarm system, seemed reasonable.

It was also necessary. Currently there are no medications to quickly relieve suicidal thoughts. Antidepressants can take a month or longer to ease depression, and many psychiatrists today believe, like Shneidman, that depression and suicidal ideation are separate conditions. Treating depression might not even address suicidal thinking. A medication that specifically targets suicidal ideation—quickly—could be lifesaving.

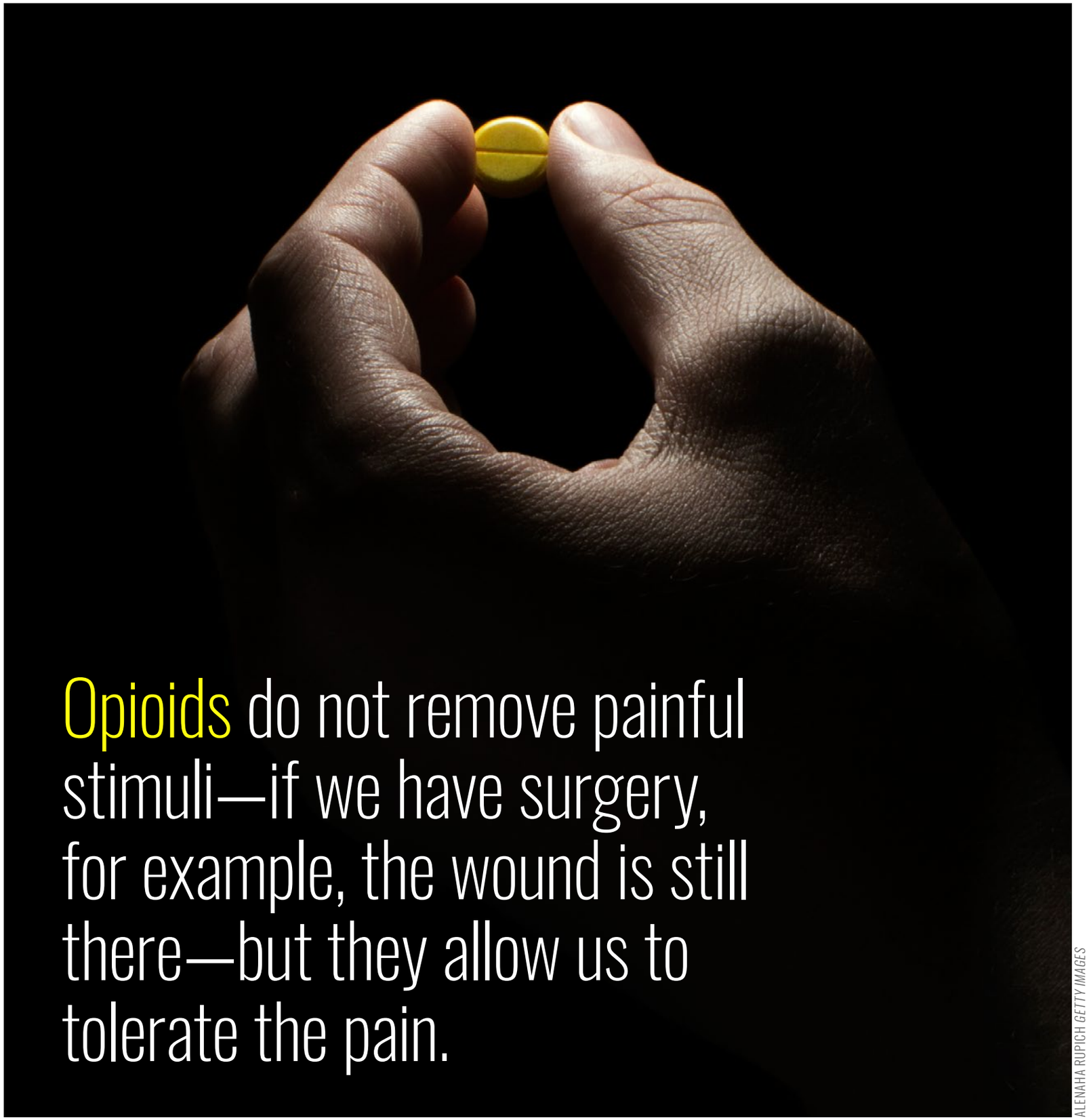
Buprenorphine, sold as Subutex in pure form and as Suboxone when combined with naloxone (which decreases its abuse potential), is an unusual opioid in that it stimulates some, but not all, of the brain's opioid receptors. It causes less euphoria than opioids such as hydrocodone, an active ingredient in Vicodin, and hydromorphone, the active ingredient in Dilaudid, but relieves pain and withdrawal symptoms. In fact, it was developed as a treatment for opioid addiction. Because it is less pleasurable, it is less likely to be abused, and because it is weaker, patients are less likely to overdose. Individuals who do abuse buprenorphine get high by crushing the tablets and injecting a solution made from the powder. Yovell and his colleagues used a gelatin-based lozenge that dissolves under the tongue to make that impossible.

The researchers recruited patients from four hospitals in Israel and assigned them to receive tiny doses of buprenorphine or placebo. At the outset, the subjects were quite ill; most of them had made suicide attempts in the past, and 57 percent met criteria for borderline personality disorder, which is characterized by chronic suicidal ideation and rejection sensitivity—meaning that mild slights can cause one's mood to plunge. The Beck Scale for Suicide Ideation was used to rate how suicidal patients were before, during and after the intervention.

The authors found a significant drop in suicidal thinking in the buprenorphine group versus the placebo group. Buprenorphine had a positive effect on depression, but the impact on suicidal thinking was even greater. Further, patients who met criteria for borderline personality disorder benefited even more than patients with depression alone. For the investigators, this finding closed a loop: extreme distress over real or perceived abandonment is a hallmark of borderline personality disorder. In borderline patients, suicidal thoughts may emerge when their highly sensitive separation-distress systems are activated, with a drop in endogenous opioids and subsequent mental pain. The robust improvements in suicidal ideation in borderline patients suggested that buprenorphine treats the psychache associated with abandonment and rejection.

The study could not *prove* that opioids treat mental pain—it was not designed to do so—but it did show that buprenorphine decreases suicidal ideation. Perhaps the study's most important contribution is its implication that treatments that help us withstand mental pain may prevent suicide.

Shneidman's original paper noted that suicide occurs when psychache has become unbearable but that individuals vary in how much pain they can bear. It follows that one can intervene with suicidal patients in two ways—decreasing pain or increasing tolerance. Shneidman believed that psychache derives from "frustrated needs" and that the therapist's task was to identify and at



ALENAHA RUPICH *GETTY IMAGES*

least partially satisfy those needs. The success of buprenorphine in decreasing suicidal ideation suggests an alternative approach. Opioids do not remove painful stimuli—if we have surgery, for example, the wound is still there—but they allow us to tolerate the pain.

Whether or not buprenorphine is ever developed as a treatment for suicidal ideation may depend on our current national attitude toward opioid use and abuse. Opioids, once marketed to physicians as the first and perhaps most humane response to complaints of pain, have been recast as a treatment best reserved for the terminally ill. Last year, in response to an epidemic of prescription opioid abuse, the U.S. Centers for Disease Control and Prevention took the unusual step of developing prescribing guidelines for the management of chronic pain. Physicians may be unwilling to prescribe opioids for nonapproved indications.

But Yovell and his colleagues' study provides a rationale for thinking about opioids in a new way. More than that, it suggests that interventions that increase our capacity to tolerate mental anguish may have a powerful role in suicide prevention. **M**

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OPINION

Does Living in Crowded Places Drive People Crazy?

A new theoretical tool called life history theory offers an answer

By Oliver Sng, Steven Neuberg, Michael Varnum, Douglas Kenrick

You may be thinking: Yes, living under crowded conditions surely drives people crazy. And the reason may be traced back to some unfortunate rats.

In the mid-20th century ethologist John Calhoun wanted to see how overcrowding would influence social behavior in rats. He placed rats in a confined space and allowed them to multiply with relatively little control. The results looked like scenes out of a horror movie: cannibalism, dead infants and complete social withdrawal, to name a few.

Calhoun's rats captured public imagination and inspired a surge of research on the psychological effects of density in our own species. Some studies found that people living in crowded environments indeed showed a variety of social pathologies, just like Calhoun's rats. But other studies did not. Reviews of the early research concluded that popular fears about overcrowding may be unfounded.

Now half a century has passed, and the world population has doubled. On the other hand, research on the psychological effects of density has all but disappeared.

We revisited this old topic in a recent paper, this time with a tool called life history theory. It is about how all animals allocate their limited time and energy across life's tasks, such as growing, mating and parenting. Aspects of the environment shape these allocation choices.

What does this have to do with density? One of life history theory's earliest ideas was that environments of low density—where there are few individuals around—would favor organisms that adopt a "fast" life history strategy. This strategy focuses on quick reproduction and having many offspring but with little investment in each. Put simply, it is focused on the present and prioritizes "quantity over quality."

A low-density environment favors a fast strategy because it is presumed to have abundant resources with little social competition. Here fast reproduction would allow for full exploitation of the environment's resources. Animals living in low-density environments also would not need to invest much in offspring, because it would be easy for those offspring to survive independently in such an environment.

But things get different when the environment gets crowded and strong social competition for resources and territory exists. To successfully compete, individuals now need to spend more time and energy building their own abilities. This often leads to a delay in reproduction. In a dense environment, one's offspring also face greater social competition. Hence, it may be more adaptive to focus time and energy

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Michael Varnum is assistant professor of psychology at Arizona State. He studies how culture shapes fundamental psychological processes ranging from empathy to conformity to self-construal.

Douglas Kenrick is professor of psychology at Arizona State. His current research interests pursue mainly questions related to evolutionary social cognition as well as links between evolutionary psychology and dynamical systems perspectives.

on just a few offspring (to increase *their* abilities and competitiveness) instead of spreading resources over many offspring.

This approach is referred to as a "slow" life history strategy, and it prioritizes "quality over quantity." A slow life history strategy also involves a psychology that plans for the future, given the need to build one's abilities over time. Our question was therefore a simple one: Would higher densities also lead *people* to adopt a slower life history?

We examined this idea in a variety of ways. First, we gathered data on country-level population densities and on a variety of psychological traits and behaviors related to life history. We did the same thing for the 50 U.S. states, where equivalent data were available.

Indeed, we found that across countries and across U.S. states, individuals in regions with denser populations showed traits that corresponded to the psychological profile of a slower life history. They were more likely to plan for the future, preferred long-term, committed romantic relationships, married later, had fewer children, and were more likely to invest in both their own and their children's education. These relationships held when taking into account alternative factors, such as economic development and urbanization.

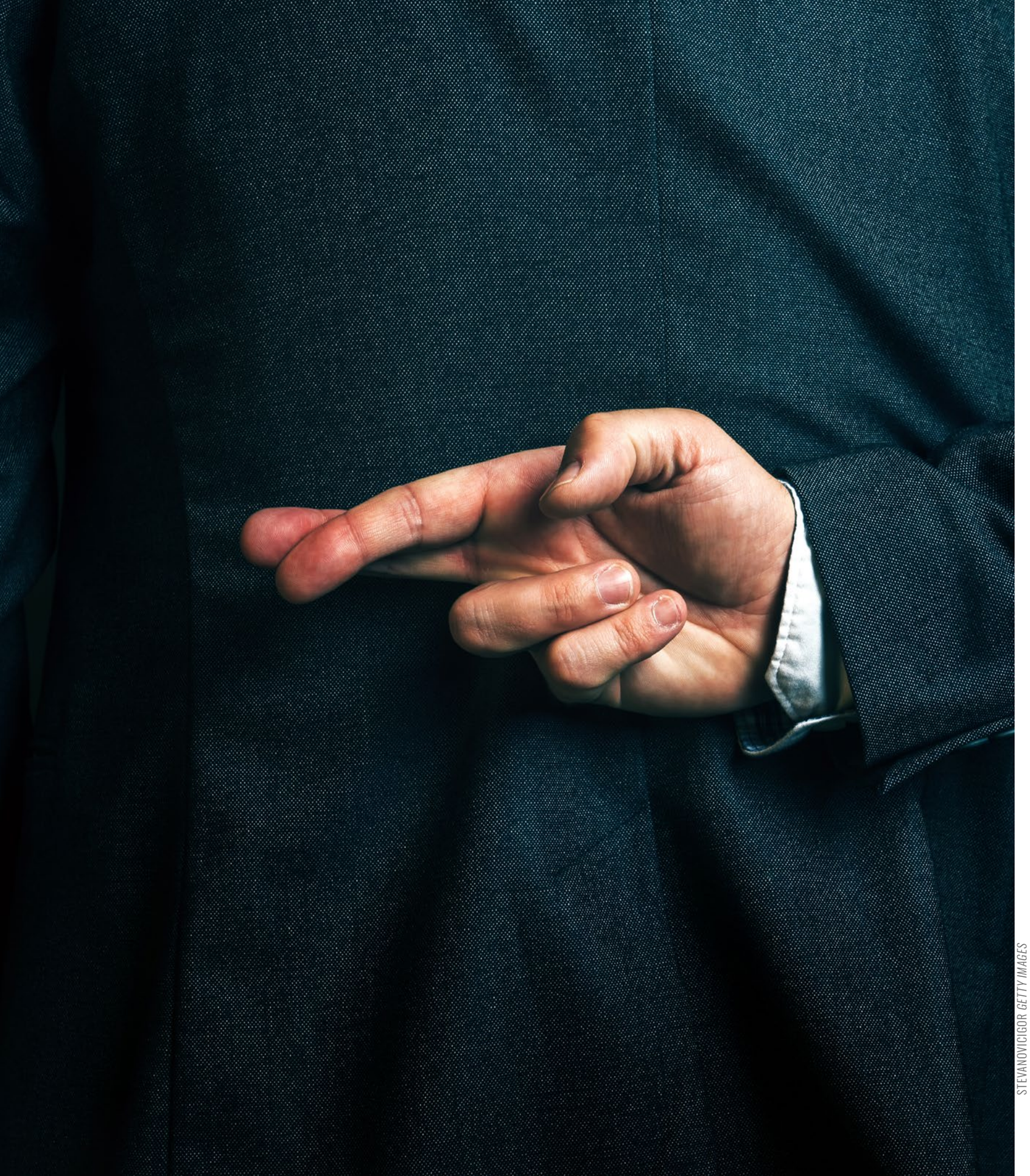
To see if there might be similar effects in short-term situations, we conducted experiments in which we had both undergraduates and slightly older adults read an article that talked about increasing population growth in the U.S. After reading the article, participants reported both their romantic relationship and family-size preferences. We found that the undergraduates who read the density article preferred having a few committed romantic relationships (instead of many casual ones). The older adults who read the same article preferred to have fewer children and to invest more in each child (instead of investing less in many children).

Thus, in experiments, individuals led to think about increasing population densities also seemed to shift toward a slower life history, characterized by quality over quantity.

Many of us have intuitions about the effects of crowdedness. It is therefore useful to anticipate some questions. For instance, will higher densities always lead to a slow life history? No. In fact, when high densities are paired with unpredictable death or disease, life history theory predicts that a faster life history will emerge. A second critical point to consider is the nature of social competition. The assumption is that humans typically compete for resources by building skills and abilities (for example, through education). But this might not always be the case. In environments where competition is carried out by forms of lethal violence, we would once again expect higher densities to lead to a faster life history.

These are just some of the many unanswered questions about density. More important, our current work presents a new way of thinking about and understanding the psychological effects of population density. In addition, it elucidates how population density might underlie psychological differences across societies and human groups in general. The hope is that our research will generate renewed interest in the study of density's psychological impact.

That said, perhaps a crowded life does drive people a little crazy—but not in the dystopian ways we expected from Calhoun's rats. Instead it may make people obsessed about planning for the future, getting a good education, waiting for that perfect romantic partner and putting everything they have into that one child who is going to make them proud. M



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OPINION

How the Science of "Blue Lies" May Explain Trump's Support

They are a very particular form of deception that can build solidarity within groups

By Jeremy Adam Smith

Donald Trump tells lies.

His deceptions and misleading statements are easy to unmask. In one example—among hundreds of well-documented lies—FBI director James Comey told Congress in March that there is "no information that supports" Trump's claim that President Barack Obama tapped his phone.

But Trump's political path presents a paradox. Far from slowing his momentum, his deceit seemed only to strengthen his support through the primary and the national election. Now every time a lie is exposed, his support among Republicans does not seem to waver very much. In the wake of the Comey revelations, his average approval rating mainly held at around 40 percent.

This has led many people to ask themselves: How does the former reality-TV star get away with it? How can he tell so many lies and still win support from many Americans?

Journalists and researchers have suggested many answers, from a hyperbiased, segmented media to simple ignorance on the part of GOP voters. But there is another explanation that no one seems to have entertained. It is that Trump is telling "blue lies"—a psychologist's term for falsehoods, told on behalf of a group, that can actually strengthen bonds among the members of that group.

ALBERTO RUGGIERI *GETTY IMAGES*

Children start to tell selfish lies at about age three, when they discover adults cannot read their minds: *I didn't steal that toy. Daddy said I could. He hit me first*. At around age seven, they begin to tell white lies motivated by feelings of empathy and compassion: *That's a good drawing. I love socks for Christmas. You're funny*.

Blue lies are a different category altogether, simultaneously selfish and beneficial to others—but only to those who belong to your group. As University of Toronto psychologist Kang Lee explains, blue lies fall in between generous white lies and selfish "black" ones. "You can tell a blue lie against another group," he says, which

makes it simultaneously selfless and self-serving. "For example, you can lie about your team's cheating in a game, which is antisocial but helps your team."

In a 2008 study of seven, nine and 11-year-old children, Lee and his colleagues found that children become more likely to endorse and tell blue lies as they grow older. For example, given an opportunity to lie to an interviewer about rule breaking in the selection process of a school chess team, many were quite willing to do so, older kids more than younger ones. The children telling this lie did not stand to selfishly benefit; they were doing it on behalf of their school. This line of research finds that black lies drive people apart, white lies draw them together and blue lies pull some people together while driving others away.

Around the world, children grow up hearing stories of heroes who engage in deception and violence on behalf of their in-groups. In *Star Wars,* for example, Princess Leia lies about the location of the Rebels' "secret base." In the Harry Potter novels (spoiler alert!), the entire life of double agent Severus Snape is a lie, albeit a blue one, in the service of something bigger than himself.

That explains why most Americans seem to accept that our intelligence agencies lie in the interests of national security, and we laud our spies as heroes. From this perspective, blue lies are weapons in intergroup conflict. As philosopher Sissela Bok once said, "Deceit and violence—these are the two forms of deliberate assault on human beings." Lying and bloodshed are often framed as crimes when committed inside a group—but as virtues in a state of war.

This research—and these stories—highlights a difficult truth about our species: we are intensely social creatures, but we are prone to divide ourselves into competitive groups, largely for the purpose of allocating resources. People can be prosocial—compassionate, empathetic, generous, honest—in their group and aggressively antisocial toward out-groups. When we divide people into groups, we open the door to competition, dehumanization, violence—and socially sanctioned deceit.

"People condone lying against enemy nations, and since many people now see those on the other side of American politics as enemies, they may feel that lies, when they recognize them, are appropriate means of warfare," says George Edwards, a political scientist at Texas A&M University and one of the country's leading scholars of the presidency.

If we see Trump's lies not as failures of character but rather as weapons of war, then we can come to see why his supporters might view him as an effective leader. From this perspective, lying is a feature, not a bug, of Trump's campaign and presidency.

Research by Alexander George Theodoridis of the University of California, Merced, Arlie R. Hochschild of the University of California, Berkeley, Katherine J. Cramer of the University of Wisconsin–Madison, Maurice Schweitzer of the University of Pennsylvania and others have found that this kind of lying seems to thrive in an atmosphere of anger, resentment and hyperpolarization. Party identification is so strong that criticism of the party feels like a threat to the self, which triggers a host of defensive psychological mechanisms.

For millions and millions of Americans, climate change is a hoax, Hillary Clinton ran a child sex ring out of a pizza parlor and immigrants cause crime. Whether they tru-

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ly believe those falsehoods or not is debatable—and possibly irrelevant. The research to date suggests that they see those lies as useful weapons in a tribal us-against-them competition that pits the "real America" against those who would destroy it.

It is in blue lies that the best and worst in humanity can come together. They reveal our loyalty, our ability to cooperate, and our capacity to care about the people around us and to trust them. At the same time, blue lies display our predisposition to hate and dehumanize outsiders and our tendency to delude ourselves.

This hints at the solution, which starts with the idea that we must appeal to the best in one another. While that may sound awfully idealistic, the applications of that insight are very concrete. In a new paper in the journal *Advances in Political Psychology,* D. J. Flynn and Brendan Nyhan, both at Dartmouth College, along with Jason Reifler of the University of Exeter in England, summarize everything science knows about "false and unsupported beliefs about politics."

They recommend a cluster of prosaic techniques, such as presenting information as imagery or graphics instead of text. The best combination appears to be graphics with stories. But this approach runs up against another scientific insight, one that will be frustrating to those who would oppose Trump's lies: who tells the story matters. Study after study shows that people are much more likely to be convinced of a fact when it "originates from ideologically sympathetic sources," as the paper says—and it helps a lot if those sources look and sound like them.

In short, it is white conservatives who must call out Trump's lies if they are to be stopped.

What can the rest of us do in the meantime? We must make accuracy a goal, even when the facts do not fit our emotional reality. We start by verifying information, seeking out different and competing sources, cultivating a diverse social network, sharing information with integrity—and admitting when we fail. That is easy. But the most important and difficult thing we can do right now, this line of research suggests, is to put some critical distance between us and our groups—and so lessen the pressure to go along with the herd.

Donald Trump lies, yes, but that does not mean the rest of us, his supporters included, need to follow his example. M

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OPINION

Why Psychiatry Needs Neuroscience

An influential subset of psychiatrists argue—absurdly—that neuroscience has little clinical relevance

By Daniel Barron

In April, *JAMA Psychiatry* published a groundbreaking addition to its lineup: an educational review intended to educate psychiatrists about neuroscience. A group of psychiatrists led by David Ross of Yale University described how and why post-traumatic stress disorder (PTSD) should be clinically evaluated from a neuroscience framework. The fact that this editorial was published in one of psychiatry's leading journals is no small feat.

Psychiatry houses a large and powerful contingency that argues that neuroscience has little clinical relevance. The relevance of neuroscience to psychiatry was the subject of a recent op-ed debate in the *New York Times*: "There's Such a Thing as Too Much Neuroscience" was rebutted by a letter under the print headline "For More Neuroscience" ("More Neuroscience, Not Less" in the online version). This specific debate—and the dense politics as a whole—exists because competing frameworks are vying for competing funding, a conflict that predates Sigmund Freud's departure from neurology.

That the relevance of neuroscience to psychiatry is still questioned is blatantly outlandish: What organ do psychiatrists treat if not the brain? And what framework could possibly be more relevant than neuroscience to understanding brain dysfunction?

In the review, Ross and his colleagues tactfully presented their case for neuroscience, describing the obvious choice for a clinical framework as one "perspective," thus making a delicate intellectual curtsey while supporting their assertions with data.

The researchers discussed five "key neuroscience themes" (read: lines of evidence from burgeoning subfields) relevant to understanding and treating PTSD: fear conditioning, dysregulated circuits, memory reconsolidation, and epigenetic and genetic considerations. Each theme accounts for the diverse biological, psychological and social factors involved in PTSD—which is to say, these factors all have some effect on the brain's mechanisms. Most important, Ross's group described how a mechanistic approach allows clinicians to trace the specific causes of PTSD to specific treatments that can target those causes.

The delicate balancing act that Ross et al. performed reflects a conflict between competing clinical frameworks, which, in turn, boil down to two different worldviews: one is intuitive; the other is data-driven. How and why these perspectives clash is better felt than explained. Perhaps I may explain the way I once felt.

The first time I saw a Purkinje cell, I was a high school sophomore in AP Biology. My teacher, Mr. Francom, had just explained that the Purkinje cell is a brain neuron and that, from a central nub, its arms splay throughout the cerebellum, connecting with other neurons. Similar connections throughout the brain formed the hardware for mental phenomena—our abilities to move, think, love, remember, and so on. Experiments and data were involved.

Following this teaser, Mr. Francom slid the Purkinje cell transparency onto the projector with a magician's élan, revealing an eerie monstrosity: a fluorescent green cell. With its long, dendritic tentacles, it seemed less like something you'd find between your ears and more like *The War of*

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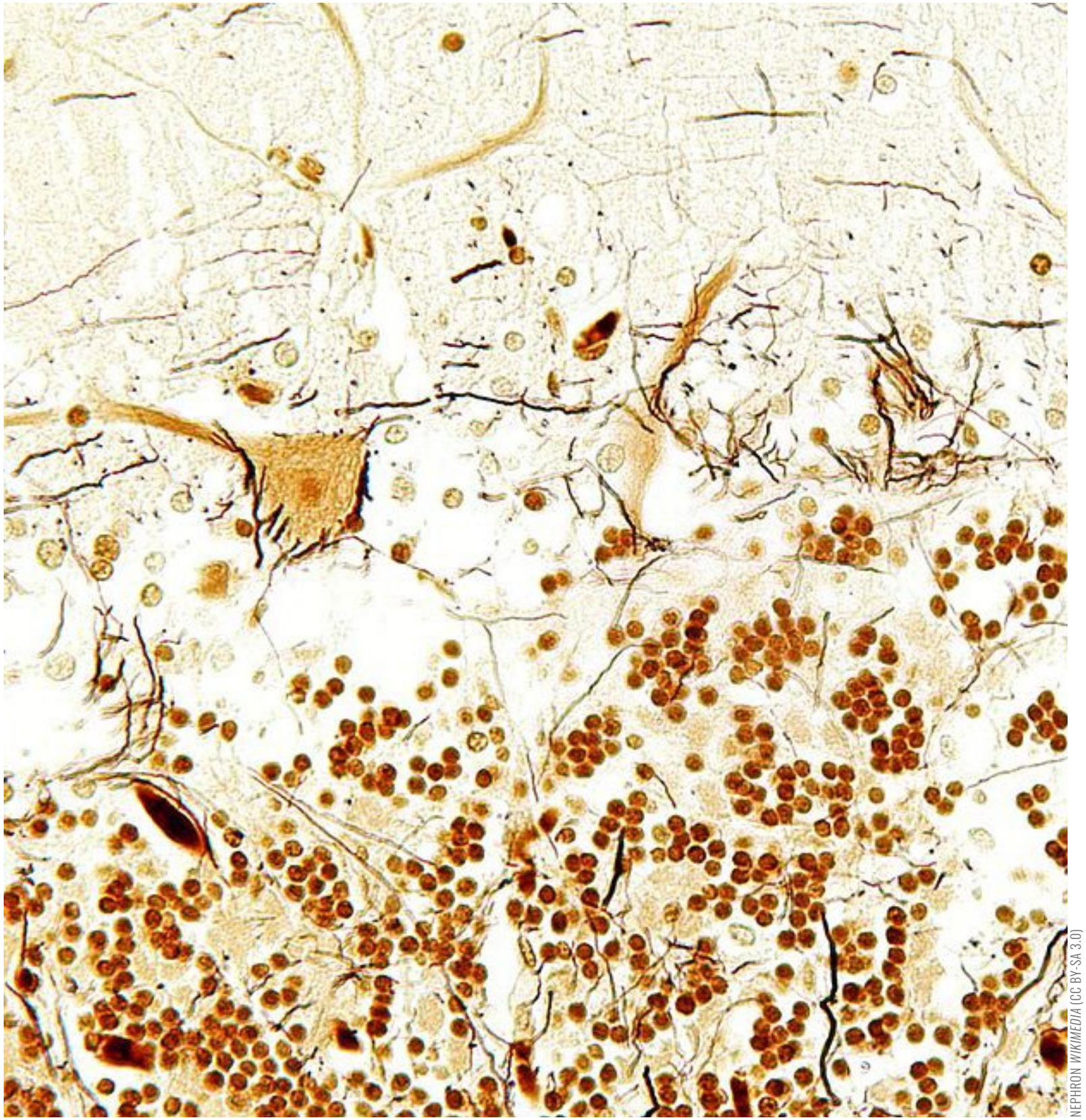

NEPHRON *WIKIMEDIA* (CC BY-SA 3.0)

the Worlds meets the Kraken.

I'm sure I blurted out, "That thing lets me think?"

The Purkinje cell was an uncomfortable disconnect from my intuition of what makes me *me*. Were my thoughts and feelings and memories all some extension of a tentacled neuron?

There was a palpable threat to realizing that my mental behavior, the phenomenon of *me,* was produced by venomous-looking neural hardware—as if someone had pulled back the magician's sleeve to reveal my own secret, destroying the beauty of my mental life.

Of course, that was just adolescent silliness. The beauty of the brain remains that it actually works, that combinations of lipid membranes, saltwater and proteins *actually do* produce the love I feel toward my wife or my experience of a sunset while zipping home on my Vespa. And yet it isn't in-

It challenges our intuition to think that brain neurons like these are responsible for all our thoughts, emotions and mental disorders—but they are.

tuitive at all that this neural hardware exists. Would you have assumed your thoughts came from a Purkinje cell?

Knowledge of the brain's hardware is even more relevant when things go awry, especially to understand specific phenomena that patients report as symptoms in mental illness.

In a recent *Molecular Psychiatry* article, Michael Treadway and Chelsea Leonard, both at Emory University, discussed the distinction between a patient's reported symptom and that patient's underlying neural hardware, which they referred to as the neural "substrate." More than a scholastic exercise, this distinction is a clinical tool that allows greater clinical precision because symptoms can have multiple causes.

Imagine it is 3 A.M., and a patient enters the emergency room reporting "chest pain." The doctors will know that this a serious symptom with many causes and that to treat the patient, they must correctly diagnose and treat the underlying cause. They will immediately examine the patient and order an electrocardiogram to see if the heart's electrical activity has changed, revealing a heart attack. They will draw blood to look for evidence of heart damage or clot formation. They will order a chest x-ray to rule out pneumonia or a broken rib.

Anxiety is also a cause of chest pain. After ruling out life-threatening causes, the doctors learn that while in the food court at a local mall, the patient broke out in a sweat, her vision blurred and her chest tightened. If she further reports that this happens every time she goes to a large public space, the doctors might diagnose her with a panic attack produced by agoraphobia, a fear of open public spaces.

But consider if our patient recently immigrated from Syria and last year was shopping with her family in a city marketplace when a car bomb exploded. PTSD now becomes the leading diagnosis.

And yet PTSD, agoraphobia and panic attacks are not causes. They are phenomena. Anxiety is a symptom, an anthropomorphism of the phenomenon produced by a network of millions, if not billions, of tentacled neurons firing together.

Ross's paper helps us understand that patients with PTSD have an overactive sympathetic nervous system, which contributes to symptoms such as hyperarousal, hypervigilance and accentuated startle response, symptoms that can spiral into a panic attack. Further refining our scope to the overproduction of adrenaline in the hypothalamic-pituitary-adrenal axis guides the clinician to prescribe propranolol and prazosin. These medications block aspects of the adrenergic system, thus targeting specific mechanisms that alleviate PTSD symptoms.

Treadway and Leonard would view Ross's system as substrate-centered, one wherein mental phenomena are followed to, and treated at, their root cause.

Treating a person by focusing on a single receptor—in the case of prazosin, the alpha-1-adrenergic receptor subtype—is not a cold, dehumanizing abstraction. By looking beyond the phenomena of our inner experience to the Purkinje cells hard at work, we can create a pragmatic, nuts-and-bolts method of understanding and healing ourselves.

Plus, studies show that it works. **M**

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