MALE STRESS, FEMALE STRESS: WHY THEY ARE NOT THE SAME *page 58*

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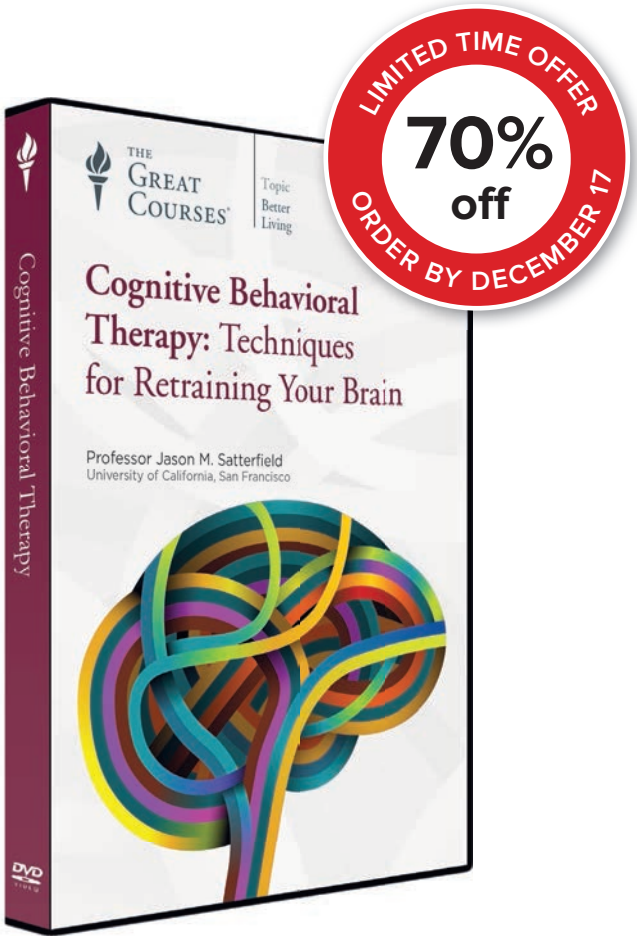

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COVER PHOTOGRAPH AND THIS PAGE: AARON GOODMAN

FROM THE EDITOR

If you are caring for an elderly or ailing relative, you are not alone. Nearly one out of five American adults serves as a caregiver to a loved one—an elderly parent or in-law in almost half of cases but in other instances a spouse, a child or other relative who has become sick or disabled. As the population ages, even greater numbers of us will assume these duties. It can be a tough job, no matter how strong the bond between caregiver and receiver. Decades of research tally the toll: poorer health, financial sacrifice, depression and anxiety.

Many who are struggling with these familial duties may be unaware that caregiving is an active subject of research, replete with revelatory findings and research-based approaches that could lighten the load or at least make it easier to bear. In our cover story, "The Givers," beginning on page 28, journalist Francine Russo walks us briskly through that research, introducing us to a variety of families along the way. Social scientists, she writes, "have identified specific strategies that can help caretakers manage the burdens and maximize the rewards of their role." Russo also offers a tip box on how to manage stress (*page 36*).

Stress—and its biological effects—is itself a lively area of scientific inquiry. In an article starting on page 58, neuroscientist Debra A. Bangasser of Temple University describes surprising biological differences in how male and female animals respond to stress. These discoveries could help explain why women have far higher rates of such stress-related conditions as post-traumatic stress disorder and depression than men do and why their reactions to drug treatment can differ. "In fact," Bangasser says, "some of the most promising new therapies under investigation—including oxytocin for anxiety and ketamine for depression—appear to have very different effects in females than in males."

Sex differences in neural activity are just part of our emerging understanding of the brain's complexity. Old binary notions that sleep and wakefulness are all-or-nothing conditions are falling by the wayside, as detailed in this issue's column by neuroscientist Christof Koch (*page 20*). The same is true for consciousness, where—as ethicist Joseph J. Fins and neurologist Nicholas D. Schiff demonstrate—investigators are finding more shades of awareness than we once knew (*page 44*). There is dazzling beauty and wonder in all this complexity. For proof, I invite you to turn to page 52 and explore our extraordinary photo gallery, "The Art of Neuroscience."

Claudia Wallis
Managing Editor
MindEditors@sciam.com

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SCIENTIFIC AMERICAN MIND

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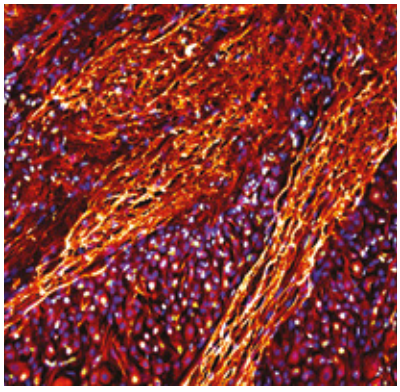

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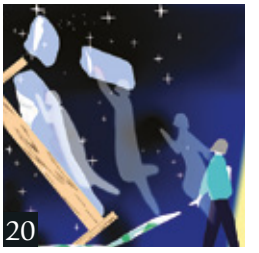
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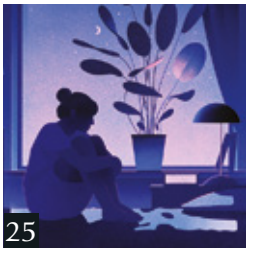
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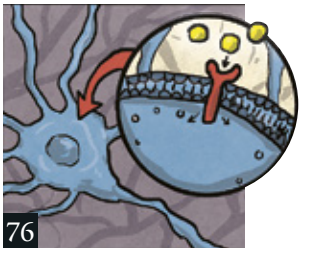
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EMOTIONAL PROTECTION?

"Banking against Alzheimer's," by David A. Bennett, provides a fascinating perspective, showing that the etiology of Alzheimer's disease and dementia in general is very complex, much like depression and schizophrenia. I wonder if researchers should investigate protective factors beyond the cognitive, such as aspects of emotion, which are increasingly recognized as part of the integrated function of the brain. Larger social networks, finding meaningful purpose in life, musical inclination and the motivation to start learning a second language may all be summed up as evidence of a positive emotional drive.

In addition, late-life depression has been associated with an increased risk of all-cause dementia, emphasizing the role that affective disturbances can play in our cognitive health. Perhaps emotional well-being can supply a buffering role against the harms of neuropathology.

Rowena Kong
via e-mail

BATTLING NEARSIGHTEDNESS

In 1990 an optometrist who specialized in vision therapy told me that he and his father, also an optometrist, had been for years tracking the statistics on the close correlation of earlier mandatory schooling with younger eyes needing prescription lenses. He said that children were being given "close work" (and this was before handheld electronic devices) when they should have been outside walking along fence tops, swinging from vines, playing hopscotch—gross motor play. I doubt he knew about the connection of sunlight with lessening of myopia, as Diana Kwon explains in "Losing Focus," but he was on the right track. The trending decline in recess periods (especially outdoors) in schools needs to be reversed for many reasons.

Michele Bartlett
Littleton, Colo.

Kwon talks about how sunlight can reduce the likelihood of a child developing myopia. Does it depend on the wavelength of the light? Does it have to be white light? Will blue, for instance, of the same intensity work as well? Is UV required?

What happens if the child wears sunglasses? Is the positive effect of the sunlight reduced? If so, we'll have to look at the risk of myopia compared with the risk of harming the eyes with overly bright light.

Ted Grinthal
Berkeley Heights, N.J.

KWON REPLIES: *Research suggests that color does matter. Scientists have found that chicks and guinea pigs that grow up under red light become nearsighted, whereas those raised under blue light do not. Some studies show that rearing chicks in blue light can even induce hyperopia (farsightedness caused by an eyeball that is too short). Sunlight contains more blue wavelengths than indoor lighting, pointing again to the importance of sending children outdoors to prevent myopia.*

As far as I can tell, researchers have yet to compare the effects of wearing sunglasses to not wearing them, but keeping them on is probably a good idea. Excessive exposure to UV light can damage the eyes and increase the risk of conditions such as cataracts.

CONSIDER THE ANIMALS

The article "Mind over Meat," by Marta Zaraska, was quite interesting, especially the techniques employed by us meat eaters to reduce our cognitive dissonance over eating animals we profess to care about. I

believe, however, that she missed an effective technique, which I employ. These animals would not be living in the first place were it not for us meat eaters. So their lives and their meat are going to waste if we do not eat them. Their care and killing should be strictly regulated, not only so that their short lives can be more comfortable but also for the health of us humans.

Doug Griffith
via e-mail

Thank you for the article on the cognitive dissonance involved in eating meat. I wonder to what degree history may play into the creation of such different terms and practices to assist in dissolving the meat-eating paradox.

For example, the Norman conquest in England may well have separated meat-eating terms into French and Anglo-Saxon, perhaps reflecting the distribution of labor (Anglo-Saxon herders and Francophone eaters). When it's on the hoof, it's "sheep" (a word with Germanic roots); when it's on the table, it's "mutton" (from the French). Likewise with "pig" (Anglo-Saxon) and *porcus* (Latin, the progenitor of French); "cow (ox)" (Old English) and *bouef* (French).

In German, there appears to be no effort to dissolve the cognitive dissonance into "eating" and "noneating" stuff. *Fleisch* is both "flesh" and "meat." Disambiguation occurs by way of added nouns: *Pferdefleisch* ("horseflesh"), *Rindfleisch* ("beef") but also *Menschenfleisch* ("human flesh").

Reinhold Schlieper
Palm Coast, Fla.

INMATES NEED MENTAL CARE

I just read "Finding His Wings," by David J. Hellerstein [Cases]. The analyses of behavioral-activation and cognitive-behavioral therapy were insightful. As a psychology student, as well as an inmate currently incarcerated in a system where mental health continues to be a hot-button topic, it gave me a look at what exactly is *not* being done to engage individuals in rehabilitative programs who struggle with mental illness. The infrastructure of mental health treatment in the prison system is inexplicably flawed, to say the least. For those inmates who eventually are paroled, they reenter society with no definitive progress in regard to their mental well-being. Can we as human beings continue to turn a blind eye to this subject?

Joseph Kelly
Pleasant Valley State Prison
Coalinga, Calif.

WHY TIME FLIES

Regarding the answer to "Why does time seem to speed up with age?" in Ask the Brains, I suggest that we perceive time relative to how long we have lived. When you are two years old, another year adds 50 percent to your life. When you are 50, another year has added only 2 percent. There is also the fact that a day when you are two years old is full of new things. A day at 50 has very few, if any, new experiences or information.

Shane Kennedy
Balbriggan, Ireland

CONCERNS ABOUT STATINS

I just read the answer to "Do statins produce neurological effects?" in Ask the Brains. I am continually hearing negative news about long-term uses of statins. I tried confronting my doctor at the VA about this because I have been taking them for going on 18 years. His reply was that the benefits far outweigh the side effects. I am not sure I believe him, but studies are so easily sensationalized that I am looking for something conclusive.

I am experiencing an increase in muscle aches and fatigue at 68 years old, and I wonder if I discontinue statins on my own if they would stop.

Jay Clark
via e-mail

THE EDITORS REPLY: *Research shows that for people who have high cholesterol, taking a statin can help prevent a heart attack or stroke. That said, there are different types of drugs and treatment approaches available, and if you feel that you are experiencing negative side effects, it is always worth discussing it with your doctor or seeking a second opinion.*

ERRATUM

In "Would You Vote for a Psychopath?" by Kevin Dutton [September/October 2016], the "Psychopathic Leader Board" box contains an error: Bernie Sanders's total score should be 129, not 139 as printed.

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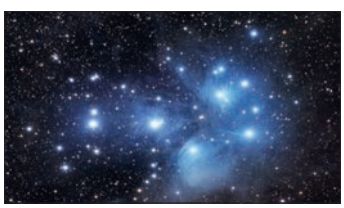

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A USER'S GUIDE TO THE BRAIN

'Tis the Season

HERE COME THE HOLIDAYS

This season brings varied and complex emotions: joy and nostalgia, love and loneliness. New research helps to explain how these feelings affect us—with some practical implications for making the season brighter and more meaningful.

ILLUSTRATIONS BY BRIAN STAUFFER

The More Rituals the Merrier

Family traditions of any type boost enjoyment of gatherings

Some people go home for the holidays hoping just to survive, burying their attention in their phones or football to avoid conflict with relatives. Yet research now suggests that is the wrong idea. Family rituals—of any form—can save a holiday, making it well worth the effort of getting everyone in the same room.

In a series of studies to be published in the *Journal of the Association for Consumer Research*, hundreds of online subjects described rituals they performed with their families during Christmas, New Year's Day and Easter, from tree decoration to egg hunts. Those who said they performed collective rituals, compared with those who said they did not, felt closer to their families, which made the holidays more interesting, which in turn made them more enjoyable. Most surprising, the *types* of rituals they described—family dinners with special foods, religious ceremonies, watching the ball drop in Times Square—did not have a direct bearing on enjoyment. But the *number* of rituals did. Apparently having family rituals makes the holidays better and the more the merrier.

The study could measure only correlations between subjects' responses, leaving causality uncertain—Do rituals increase holiday pleasure, or do people who already enjoy the holidays choose to perform more rituals? Yet enjoyment ratings were higher when given after, versus before, describing rituals, suggesting that simply thinking about rituals can put a warm filter on one's experience.

"Whatever the ritual is, and however small it may seem, it helps people to really get closer to one another," says Ovul Sezer, a researcher at Harvard Business School and the paper's primary author. "[With] some rituals we don't even know why we do them, but they still work," she says.

It could be that rituals offer "small, nonobvious ways" to get people to share an experience without feeling awkward or forced, suggests Kathleen Vohs, a psychologist at the University of Minnesota and one of Sezer's co-authors. She compares that with "obvious ploys" such as saying, "Hey, everyone, gather around the kitchen table, we're going to play Yahtzee," which, she notes, "might be more likely to produce a whole lot of kickback."

—Matthew Hutson

Embrace the Nostalgia

The bittersweet emotion increases feelings of vitality

On holidays, it's natural to feel a longing for times gone by—a childhood spent singing carols or meals spent with now departed loved ones. Recently scientists have explored the bittersweet feeling of nostalgia, finding that it serves a positive function, improving mood and possibly mental health. A new paper illuminates why it works,

The Christmastime Suicide Myth

Rates are low before, on and after Christmas, but New Year's Day sees a spike

It seems logical that for a depressed person, the holidays might be especially tough—extra stress, loneliness and sad reminders of lost loved ones—so perhaps the popular belief that suicides spike around Christmastime is no surprise. Yet the data tell a different story. Recent studies from several countries show that rates in December and on Christmas in particular tend to be the lowest of the year, but other major holidays do see spikes, especially New Year's Day.

In one such study, suicide rates in England consistently dipped on Christmas and spiked on New Year's Day during the 15-year study period, according to the paper published in June in the *Journal of Affective Disorders*. The researchers reported an overall peak in springtime, and the highest daily rates were observed on Mondays. An older study reported a similar Christmas Day decline in the U.S., with rates up to 15 percent lower than average on that day.

Findings reported in 2015 in the *European Journal of Public Health* concur, showing about 25 percent fewer suicides around Christmastime in Austria. Rates there were particularly low on Christmas Eve and remained so until January 1, when the most suicides of any day of the year occurred. The authors also observed higher rates on Mondays and Tuesdays, as well as during the week after Easter.

There are exceptions to this trend. Australia and Mexico do see slightly elevated rates on both Christmas Day and New Year's Day (as well as on Mother's Day and Mexican Independence Day). But most nations follow the myth-busting pattern: suicide rates are lower than average around Christmas.

According to clinical psychologist Martin Plöderl, a co-author of the Austrian study at Paracelsus Medical University in Salzburg, there is typically more social connection for many people around Christmas, which is an established protective factor for suicide. Psychiatric hospital admissions also decrease during this period.

So why the spike on New Year's? Researchers suggest "the broken promise effect" may explain it—along with the increases after Easter and weekends. "Many of us are familiar with the feeling after holidays: 'Was that it? I expected more fun, more relaxation, and tomorrow I have to go back to everyday life!'" Plöderl says. "For depressed people, the broken promise of Christmas and the blank year lying ahead may increase hopelessness and thus suicide risk." The greater alcohol consumption that takes place on New Year's Eve and Day may also play a role in lowering inhibitions, and "some people may postpone their planned suicide so that their families and friends can enjoy Christmas," he explains.

Although these findings cannot speak to any particular individual's suicide risk, they have important implications for public policy and medical practitioners. The U.S. Centers for Disease Control and Prevention cautions on its Web site that perpetuating the Christmas suicide myth could hurt prevention and public awareness efforts. In addition, this misperception, Plöderl says, "may translate to less optimal discharge planning [from psychiatric care]." It might be fine for some depressed patients to be home for the holidays, but as New Year's approaches, "it would be good to offer more support." *—Tori Rodriguez*

finding that this sepia-toned sentiment does not cement us in the past but actually raises our spirit and vitality.

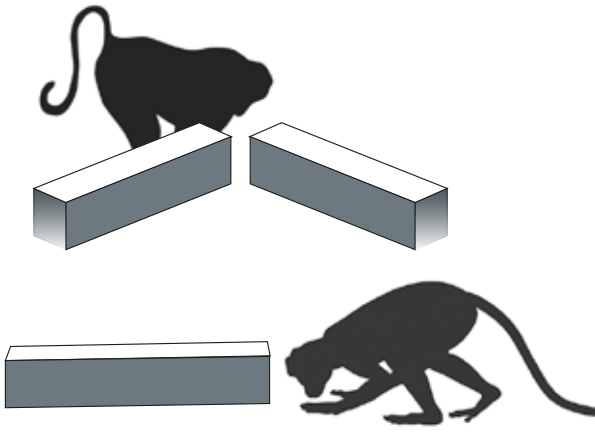
In several experiments conducted online and in the laboratory, when subjects were induced to experience wistful reverie via sentimental song lyrics or memories, they reported greater self-continuity, as measured by a validated index that asks participants how much they agree with statements such as "I feel connected with my past" and "important aspects of my personality remain the same over time." Constantine Sedikides, a psychologist at the University of Southampton in England and the primary author of the paper, which was recently published in *Emotion,* had shown this effect in a 2015 paper. But here they found that nostalgia boosted self-continuity by increasing a sense of social connectedness. Sentimental recollections often include loved ones, which can remind us of a social web that extends across people—and across time.

The researchers found this pattern in American, British and Chinese participants. They also went a step further and observed, via questionnaires about other concurrent feelings, that self-continuity brings a feeling of vitality—of "energy and spirit."

Tim Wildschut, one of Sedikides's Southampton collaborators on the paper, notes there are many ways people elicit nostalgia—looking at photographs, cooking certain meals, sharing stories or playing music. He calls the feeling, which we naturally experience several times a week, "a psychological immune response that is triggered when you experience little bumps in the road." So if you are feeling a bit discombobulated over the holidays, pull out a photo album and spend some time revisiting your past. ***—Matthew Hutson***

The Mental Gymnastics of Monkeys

Macaques join the exclusive group of animals who show metacognition—thinking about their own thoughts



When faced with two tubes hiding food, most monkeys approached the center gap. They weighed the options and chose the most efficient strategy.

Humans were long thought to have a monopoly on metacognition, which is the ability to contemplate one's own mental states. Captive apes have recently shown this skill by demonstrating that they are aware of the extent of their knowledge—they know when they are missing crucial information to solve puzzles or find food. Now a study in semiwild rhesus monkeys provides important evidence that metacognition is not the province of humans, apes or trained animals alone.

Alexandra Rosati of Harvard University and Laurie Santos of Yale University observed 120 rhesus monkeys searching for food the researchers had planted, either in one end of a single tube or in one of two tubes arranged in a **V** [*see illustration at right*]. In both cases, half the monkeys could watch as the food was planted—so they knew where it was—while the other half had their view blocked by a screen. Each monkey took part just once.

The main question is what monkeys do in the screened, two-tube case. The most efficient strategy is to peer inside the gap in the crook of the **V**, which allows them to check both tubes for the food at once, but reliably choosing that approach requires metacognition. In particular, a monkey needs to recognize that it does not know where the food is hidden, then contemplate its options and choose a course of action.

In this key condition, 27 of 30 monkeys began searching by peering inside the gap as compared with 13 in the unscreened, two-tube case—who already knew where the food was. The researchers ruled out the possibility that they were simply approaching the middle of the setup—fewer than a third in the one-tube cases approached the center. What is more, monkeys in the hidden, two-tube case took a few seconds longer to begin searching, suggesting they had reflected on what to do before acting.

"They could be randomly checking each location, but they're not," which suggests that metacognition was at work, Rosati says.

Michael Beran of Georgia State University, who studies metacognition in apes, hails the study as important new evidence: "In demonstrating that this was true in a semiwild group of monkeys, we can have greater confidence that some animals engage in metacognitive processes." —*Nathan Collins*

Weight-Loss Surgery Alters the Brain

Changes in neural activity may help explain why gastric bypass is so effective

In June, international diabetes organizations endorsed provocative new guidelines suggesting physicians should consider gastric bypass surgery for a greatly expanded number of diabetics—those with a body mass index of 30 and above as opposed to just those with a BMI of 40 or more. Research has shown that the surgery helps people lose more weight, maintain the loss longer and achieve better blood glucose levels than those who slim down by changing diet and exercise habits. Now a study in mice suggests the effectiveness of bariatric surgery may stem in part from changes it causes in the brain.

According to the study, published in the *International Journal of Obesity,* gastric bypass surgery causes the hyperactivation of a neural pathway that leads from stomach-sensing neurons in the brain stem to the lateral parabrachial nucleus, an area in the midbrain that receives sensory information from the body, and then to the amygdala, the brain's emotion- and fear-processing center.

The obese mice underwent so-called Roux-en-Y bypass surgery, in which surgeons detach most of the stomach, leaving only a tiny pouch connected to the small intestine. Shortly after the surgery, the mice begin to show increased activation in this neural pathway, along with reduced meal size and a preference for less fatty food. They also begin to secrete higher levels of satiety hormones. Similar behavioral and hormonal patterns are found in humans after bypass surgery, suggesting that the brain changes may also be similar—but the authors say looking at this particular circuit in humans with brain imaging is difficult because the resolution is not up to the task.

According to senior author Hans-Rudolf Berthoud of L.S.U.'s Pennington Biomedical Research Center, the change in brain activity is probably caused by the sudden novel contact of undigested food hitting the small intestine rather than the predigested mix that usually comes from the stomach. "These patients basically have to relearn how to eat. They were used to large portions and wolfed the food down. It was pleasurable for them. But if they do that after surgery, that hurts them," Berthoud says. The brain areas made hyperactive by the surgery probably reflect this new negative feedback, which is a powerful learning tool.

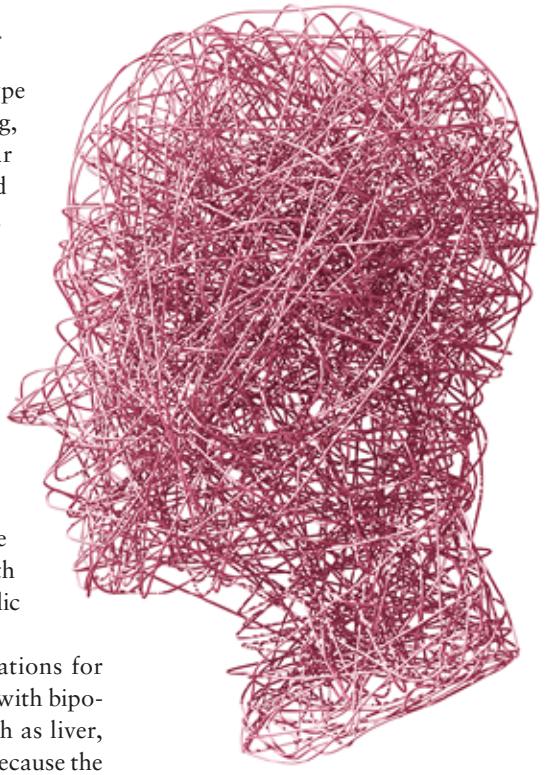
In a few weeks the pathway was no longer hyperactive in the mice, perhaps indicating that the brain recruited other processes to support reduced eating, Berthoud says. He adds that this pathway is probably only a small piece of the puzzle. Past studies suggest that bariatric surgery also affects the brain's reward system, making fatty foods less pleasurable. One question that remains is why bypass surgery does not lead to the frustratingly slow metabolism seen in people who lose large amounts of weight by drastic lifestyle changes. In a much publicized study earlier this year, researchers found that contestants on the television show *The Biggest Loser* still had a sluggish metabolism six years after their giant weight loss. Bariatric patients, according to similar studies, achieve a stable, normalized metabolism within a year.

Gastric bypass surgery is not without risks or side effects, of course. Yet as the studies pile up showing that weight loss from dieting is nearly impossible to maintain long term, Berthoud and other researchers hope to keep elucidating bariatric surgery's pros and cons. "This is a very complex story," he says. —*Meredith Knight*

GETTY IMAGES (*monkey icons and seated man*)

A New Target for Treating Mania?

Elevated levels of uric acid are implicated in bipolar disorder



Uric acid is almost always mentioned in the context of gout, an inflammatory type of arthritis that results from excessive uric acid in the blood. It may be surprising, then, that it has also been linked with a vastly different type of disease: bipolar disorder. Elevated uric acid has been observed in patients with acute mania, and reducing uric acid improves symptoms. New evidence supports its potential as a treatment target.

Uric acid is a by-product of the breakdown of compounds called purines, found in many foods and manufactured by the body. High levels of uric acid can indicate that these compounds, such as the neurotransmitter adenosine, are being broken down too readily in the body. "Adenosine might play a key role in neurotransmission and neuromodulation, having sedative, anticonvulsant and antiaggressive effects," says physician Francesco Bartoli, a researcher at the University of Milano-Bicocca in Italy. Bartoli's new study, published in May in the *Journal of Psychosomatic Research,* examined uric acid levels in 176 patients with bipolar disorder or another severe mental illness and 89 healthy controls. The results show that bipolar disorder was the only diagnosis significantly linked with levels of uric acid. Excess uric acid was found to be linked to male gender, metabolic syndrome, waist size and triglyceride levels.

Beyond the too rapid breakdown of adenosine, other potential explanations for increased uric acid include the metabolic abnormalities often present in people with bipolar disorder and frequent consumption of purine-rich foods and drinks, such as liver, legumes, anchovies and alcohol. Fructose consumption can also be a problem because the sugar inhibits uric acid excretion. Dietary interventions may reduce levels, but medication is typically required if dietary changes are insufficient.

The uric acid link points to novel treatments for mania. In a double-blind, randomized controlled trial reported in 2014, researchers in Iran and Switzerland investigated the efficacy of allopurinol, a gout medication that reduces levels of uric acid, in 50 patients with bipolar disorder during acute mania. During a period of four weeks, subjects received the mood stabilizer sodium valproate—a standard treatment—plus either allopurinol or a placebo. In the allopurinol group, there was a significant reduction in uric acid levels and mania symptoms, and rates of remission were 23 times higher.

In the future, doctors may find it useful to help bipolar patients modify their diet, says study co-author Serge Brand, a research psychologist at the University of Basel in Switzerland: "This approach is timely and is part of the broader research focusing on the so-called gut-brain axis."

—Tori Rodriguez

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(PHARMA WATCH)

Could a Diabetes Drug Help Beat Alzheimer's Disease?

Metformin may slow or reverse dementia and cognitive impairment, even in nondiabetics

Most of the 20 million people diagnosed with type 2 diabetes in the U.S. take metformin to help control their blood glucose. The drug is ultrasafe: millions of diabetics have taken it for decades with few side effects beyond gastrointestinal discomfort. And it is ultracheap: a month's supply costs $4 at Walmart. And now new studies hint that metformin might help protect the brain from developing diseases of aging, even in nondiabetics.

When nondiabetic rats are given metformin, their memory improves, thanks to an increase in neural stem cells.

Diabetes is a risk factor for neurodegenerative diseases, but using metformin is associated with a dramatic reduction in their incidence. In the most comprehensive study yet of metformin's cognitive effects, Qian Shi and her colleagues at Tulane University followed 6,000 diabetic veterans and showed that the longer a patient used metformin, the lower the individual's chances of developing Alzheimer's disease, Parkinson's disease, and other types of dementia and cognitive impairment. In line with some of the previous, smaller studies of long-term metformin use, patients in the new study who used the drug longer than four years had one quarter the rate of disease as compared with patients who used only insulin or insulin plus other antidiabetic drugs—bringing diabetics' risk level to that of the general population. The findings were presented in June at the American Diabetes Association's Scientific Sessions meeting.

Even in the absence of diabetes, Alzheimer's patients often have decreased insulin sensitivity in the brain, says Suzanne Craft, a neuroscientist who studies insulin resistance in neurodegenerative disease at the Wake Forest School of Medicine. The association has led some people to call Alzheimer's "type 3 diabetes." Insulin plays many roles in the brain—it is involved in memory formation, and it helps to keep synapses free of protein debris, including the tau tangles and amyloid plaques that build up in Alzheimer's, Craft says.

Metformin, then, may help correct insulin issues in the aging brain. Research in animals shows that the drug's effect on neural stem cells might be key. Neuroscientists Jing Wang and Freda Miller, both then at Toronto's Hospital for Sick Children, showed that when nondiabetic mice are given metformin, their memory improves, thanks to an increase in the neural stem cell population and in the number of these cells that develop into healthy neurons in the hippocampus, the brain's memory center.

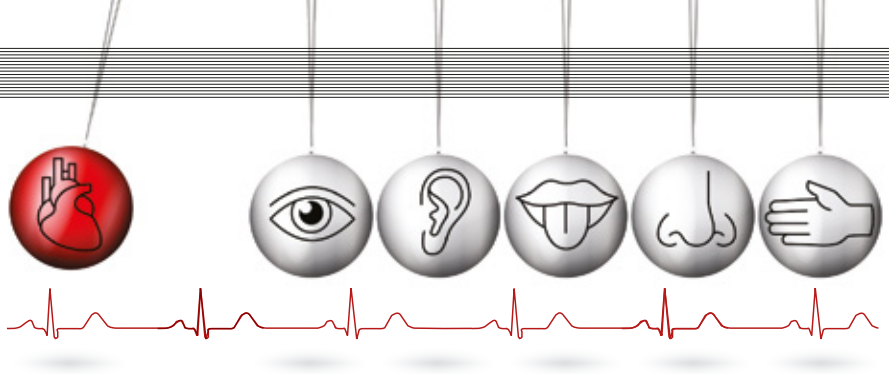
Human clinical trials also show promise in treating early Alzheimer's. Steven E. Arnold, a neurologist at Massachusetts General Hospital showed that early Alzheimer's patients had small but significant improvements in their memory and cognitive functioning after taking metformin for eight weeks as compared with a placebo. Brain imaging also revealed some improvements in neural metabolism. Such small effects are the norm when it comes to Alzheimer's; even established drugs are only modestly effective and only for a limited period. "That is one of the great motivations to find new therapies," Craft says.

Arnold hopes to run a larger trial that can better evaluate metformin's efficacy, but funding has been an issue. Because metformin is generic and cheap, drug companies have little profit motive to test it, according to Arnold. "This is a simple, common, cheap medicine that may affect an important aspect of cognitive impairment in older adults, and there's a compelling scientific reason to look at it. Now we just need to really study it in a way that will give us a clear answer as to whether it really helps," Arnold says. If the funding were in place, he believes a definitive study could be completed in two years.

Craft's and Arnold's research groups are also working to find Alzheimer's biomarkers, measurable biological signals of the disease, so that patients at high risk of developing neurodegenerative disorders could be identified early. Those patients could potentially use metformin and other insulin sensitizers to prevent its onset.

—Meredith Knight

SCIENCE SOURCE (*pill*); © ISTOCK.COM (*pills icon*)



How Your Heartbeat May Trick Your Senses

The brain reacts oddly to stimuli in sync with the heart

Can you feel your heart beating? Most people cannot, unless they are agitated or afraid. The brain masks the sensation of the heart in a delicate balancing act—we need to be able to feel our pulse racing occasionally as an important signal of fear or excitement, but most of the time the constant rhythm would be distracting or maddening. A growing body of research suggests that because of the way the brain compensates for our heartbeat, it may be vulnerable to perceptual illusions—if they are timed just right.

In a study published in May in the *Journal of Neuroscience,* a team at the Swiss Federal Institute of Technology in Lausanne conducted a series of studies on 143 participants and found that subjects took longer to identify a flashing object when it appeared in sync with the rhythm of their heartbeats. Using functional MRI, they also found that activity in the insula, a brain area associated with self-awareness, was suppressed when people viewed these synchronized images.

The authors suggest that the flashing object was suppressed by the brain because it got lumped in with all the other bodily changes that occur with each heartbeat—the eyes make tiny movements, eye pressure changes slightly, the chest expands and contracts. "The brain knows that the heartbeat is coming from the self, so it doesn't want to be bothered by the sensory consequences of these signals," says Roy Salomon, one of the study's co-authors.

Other research has previously linked our heart to our sense of self. For example, studies show that people will more readily feel that a virtual-reality body or limb is truly their own when it appears along with a stimulus that flashes in sync with their heartbeats.

On the opposite end of the spectrum are study results showing that cardiac sensations can enhance the processing of threats. Individuals detect scary images that appear in time with heartbeats more easily and find them more intense. Perhaps because a noticeable heartbeat is often linked to fear or anxiety, in this case the brain mistakes the synchronized stimulus as being linked to its internal fight-or-flight reaction. The finding helps to explain why people who are highly sensitive to their internal states, including being aware of their heart beating, tend to be more prone to anxiety and panic disorders. For most of us, however, the heart labors away unnoticed—and the related perceptual quirks may be going unnoticed, too.

—Diana Kwon

Learn to Be Happier with Second Best

When your first choice is unavailable, you may be more satisfied with something completely different

You can't always get what you want—the car is too expensive, the restaurant already full, your favorite snack sold out—but you can do your best to choose the next most appealing option. Research suggests that when making that second choice, you might end up happier if you go for something very different from what you originally wanted.

In a series of studies published in May in *Psychological Science,* researchers probed participants' preferences by tempting them with gourmet chocolate. The scientists let subjects taste the fancy brand and then offered them a choice between a similar substitute (store-brand chocolate-covered peanuts) and a radically different substitute (a granola bar). Another set of participants got the same setup, but they were allowed to try both options before choosing. In the first experiment, 73 percent chose the generic chocolate, but in the second experiment, only 52 percent did—more participants presumably had realized they would be happier with the granola bar.

In an additional experiment, participants were assigned to eat some gourmet chocolate or a bite of either substitute, and then they were asked how much they still craved the original fancy chocolate. Those who ate the store-brand chocolate ended up craving the gourmet version more than those who ate the granola bar. In fact, those who ate the granola bar craved the gourmet chocolate no more than those who ate the fancy chocolate itself.

The fact that the similar substitute was less satisfying and left a stronger residual craving suggests the existence of a "negative contrast effect," according to the researchers. "A poor replacement is worse in terms of ultimate satisfaction than something completely different that serves the same purpose," explains Carey K. Morewedge, an associate professor of marketing at the Boston University School of Management and senior author of the study.

The finding is useful for people on restricted diets. Yet researchers also think this psychological phenomenon probably applies to a lot more than just food. The next time you find yourself in a situation where the thing you really want is not available, try a wildly different option and enjoy it without a second thought. *—Jessica Schmerler*

A GUIDE TO MASTERING YOUR WORLD

How to Be a Better *forgiver*

When I first decided to write about forgiveness for this end-of-year column, I was thinking about the holidays and how a little extra forgiveness among friends and family could make this season merrier. But as I delved into the rich well of research, it dawned on me how much our larger human family needs forgiveness right now. The past 12 months have seen more than their fair share of tragedy and injustice: violence between citizens and police, terror attacks, divisive elections. So much injury has been done, and so many people have been left in grief—can the anger and trauma ever be resolved? The forgiveness researchers I talked to say that it can and that it starts with you and me learning to forgive, in both big ways and small.

#1 **Forgive for your own sake.** We often talk about forgiveness as if it's a gift to bestow on someone once they have apologized or made restitution. I suppose that paradigm works fine for everyday injuries like dinging a car door. But how could anyone *ever* make restitution for killing a person's family member or terrorizing a nation? They can't. That's why it is important to grasp that "forgiveness is for *you* and not for anyone else," says psychologist Frederic Luskin, director of the Stanford Forgiveness Project, a series of workshops and studies for people affected by everything from office politics to deadly international conflicts.

Forgiveness—deliberately letting go of negative feelings toward someone who has harmed you—appears to have significant health and wellness benefits for the person giving it. In an early seminal study, Luskin and his colleagues led a workshop for five women from Northern Ireland who had lost children to sectarian violence. After one week, not only did the women feel dramatically less hurt, their depression scores fell by 60 percent. Six months later the women reported feeling half as stressed as they had before the workshop. Many other studies since have come to similar conclusions: a 2014 meta-analysis of 54 studies linked increased feelings of forgiveness with significant reductions in depression and anxiety.

#2 **Aim for empathy.** There are several evidence-based counseling techniques meant to help people move toward forgiveness, says psychologist Everett Worthington, co-author of the 2014 meta-analysis and a longtime researcher at Virginia Commonwealth University. In his process, known by the acronym REACH, the first step is to recall the hurt that was done to you as objectively as you can. "We try to get people to look at things from the point of view of the person who hurt them and get a sense of empathy for what was going on with that person," Worthington says.

One exercise he uses to build such empathy is the empty chair dialogue, a decades-old therapeutic tool. In his version, you sit across from an empty chair and pour your heart out as if the person who harmed you is sitting right there; then, you switch seats and talk from that person's point of view about why "you" did what you did. If you can foster empathy—or even pity—for the person who hurt you, those less negative emotions will begin to edge out some of the pain and anger you feel, Worthington says.

#3 **Calm the fight-or-flight reaction.** Feelings of hurt and trauma often come in waves—and as the feelings crest, your body switches into fight-or-flight mode, Luskin says. In these moments, he recommends intervening with a simple stress-management technique such as deep breathing or a compassion meditation. This tends to work best in situations where you have had adequate time to grieve. If stress management doesn't make a dent in your suffering, he says, it's a sign that "the issue is something that really needs attention and may not be easy to tackle on your own."

#4 **Keep trying.** Forgiveness takes time. "You don't go right to forgiveness when something first happens," Luskin says. "You have to take time to let the wounds heal and allow the mind to recover from the shock." Once you are ready to try to forgive, the more time you spend endeavoring to do it, the closer you get to it, Worthington says. "The research is clear," he says. "You get about one tenth of a standard deviation closer to forgiveness for every hour you spend working on it." These findings come from professionally led workshops and therapy sessions, which are much different than trying to do it on your own, but Worthington says persistence pays off in self-help situations, too. Even just making the decision to try to forgive moves you a bit closer.

Although we may seek to forgive first and foremost for our own well-being, Worthington believes that it can have a cascading effect on the people around us and even society at large. "The more we can lower the amount of background bitterness, resentment and hostility, the fewer people are going to end up reaching their threshold and doing something that's terrible or violent." It has been a hard year, and there is much to be forgiven. Yet is it crazy to think that it can start … with each of us? —*Sunny Sea Gold*

MAGOZ (*illustration*); PAUL PANTAZESCU © *iStock.com* (*globe*)

Why We Love Moral Rigidity

We tend to trust people who adhere to moral rules, even when doing so leads to bad outcomes

Most people strictly adhere to moral rules—such as "thou shall not kill"—even when breaking them leads to a better outcome, such as sacrificing one person to save five. Is it just a bug in our ethical processing? New research points to one function of such rule following: we are more likely to trust those who abide by simple principles.

In philosophical terminology, maximizing outcomes is called utilitarian, whereas prioritizing rights and duties is deontological. A 2013 paper in *Cognition* revealed that even when people claim it is moral to, say, throw a dying man overboard to keep a life raft afloat—a utilitarian act—they view someone who does such a thing as lacking empathy and integrity. Now a paper in the June issue of the *Journal of Experimental Psychology: General* measures people's actual behavior toward those who make such utilitarian decisions.

In several experiments, psychologists Jim Everett and Molly Crockett, both at the University of Oxford, and David Pizarro of Cornell University asked American adults to respond to moral dilemmas and then interact with other supposed respondents online. When those respondents said they would push a fat man off a footbridge to block a trolley from killing five rail workers, participants rated them as less moral and trustworthy, and they entrusted them with less money in an investment game.

We don't evaluate others based on their philosophical ideologies per se, Pizarro says. Rather we look at how others' moral decisions "express the kind of motives, commitments and emotions we want people to have." Coolheaded calculation has its benefits, but we want our friends to at least flinch before personally harming others. Indeed, people in the study who had argued for pushing the man were trusted more when they claimed that the decision was difficult.

Politicians and executives should pay heed. Leading requires making hard trade-offs—is a war or a cut in employee benefits worth the pain it inflicts? According to Pizarro, "you want your leader to genuinely have or at least be really good at displaying the right kinds of emotions when they're talking about that decision, to show that they didn't arrive at it callously." Calmly weighing costs and benefits may do the most good for the most people, but it can also be a good way to lose friends. ***—Matthew Hutson***

More Immigrants, Bigger Smiles and Frowns

People are more likely to wear their emotions on their sleeve in countries with a strong history of immigration

Psychologist Paula Niedenthal was rereading *The Little House on the Prairie* series five years ago when a question came to mind: On the U.S.'s plains in the 1800s, how did the mix of cultures affect how people expressed their emotions? From demonstrative Italians to reticent Swedes, a variety of immigrant groups had to communicate during farming and trading. She wondered whether the long history of migration in the nation has influenced the way we show our feelings.

In 2011 Niedenthal found the data she needed to answer that question—the number of cultures migrating to various countries during the past 500 years—in a paper written by two economists at Brown University. Using those data, Niedenthal and her graduate students at the University of Wisconsin–Madison recently published two papers demonstrating that people from heterogeneous cultures—those with more historical immigration—display more easily recognized emotions than those from homogeneous cultures.

"If you share language and culture, you don't need to be emotionally expressive," Niedenthal says. If you do not have that common background, you would want your emotions to be obvious and get your point across.

In one of the papers to come out of Niedenthal's group, published in 2015 in the *Proceedings of the National Academy of Sciences USA,* first author Magdalena Rychlowska and her co-authors had 726 people from nine countries complete a questionnaire about how they react to different facial expressions. The researchers found that those from more historically heterogeneous cultures tend to see a smile as a good reason to be friendly or get close to someone. Those from homogeneous cultures, however, more often saw a smile as a way to demonstrate superiority. "Smiles are basically like languages—you use them in different ways," says Rychlowska, now at Cardiff University in Wales.

Expanding on that research, Adrienne Wood, a current Ph.D. candidate in Niedenthal's lab, gathered existing data on emotion recognition from 92 papers representing 82 cultures. She looked at how often subjects attributed the correct emotion to a photograph, video or audio recording and compared that with the historical heterogeneity in the expresser's country. She found that people from cultures with higher rates of immigration display more recognizable facial expressions and vocal cues. "Cultures evolve to address the particular challenges of their social and ecological environments," says Wood, whose study was published this past January in *Emotion.*

The researchers hope to investigate more census data soon, which may reveal how long it takes a heterogeneous population of people to shift the way they emote. "A long history of migration changes the whole culture," Niedenthal says. *—Susan Cosier*

GETTY IMAGES

The Case of the Oversized Planet

Illusions noticed by Galileo can help explain how we see light and dark

From Earth, Venus (*center*) appears larger than Jupiter (*far left*) because of an intriguing optical effect. The moon, viewed the same night, has been added to this image for scale.

Galileo Galilei was puzzled. The Renaissance-era astronomer had noticed that planets appeared to expand with a "radiant crown" when viewed with the naked eye—but the effect was greatly diminished when viewed through a telescope.

The discrepancy led him to wonder: Was this size illusion caused by moisture on the cornea? Light scatter? Neither possibility satisfied because these effects would persist even if one used a telescope. In fact, Galileo had hit on a visual riddle that researchers are still unraveling.

One clue came from the observations of another luminary: artist and engineer Leonardo da Vinci. Just decades before Galileo's discovery of the radiant crowns, Leonardo had noted that dark objects on a light canvas seemed more defined than light objects on a dark background. Vision scientists since have found that a white shape on a black background often appears larger than an equally sized dark object on a light background. An explanation for these peculiar perceptual patterns arrived in the 19th century, when Hermann von Helmholtz, the venerable German physicist and physiologist, determined that there were at least two contributors to this effect, which he dubbed the "irradiation illusion."

The first contributor results from the way light scatters in the eye. When we look at a very bright object, photons pass through the retina, and some are absorbed by photoreceptors, creating focused vision. Unabsorbed photons can then reflect off the back of the eye behind the retina and disperse as they reflect back through the retina, resulting in scattered, unfocused activation of a larger patch of photoreceptors. This phenomenon is called entoptic glare.

This optical effect helps to explain not only Galileo's radiant crowns but also why Jupiter, our solar system's largest planet, appears smaller than Venus. Technically, both astronomical bodies are so far away that their photons subtend an area smaller than a single photoreceptor in an Earth-bound human's retina. In fact, depending on the time of year, the planets should appear between nine and 66 arcseconds across—visual distances so small to the naked eye that a person with 20/20 vision would only perceive them as about one arcminute each. (To illustrate how small that is: if you painted your thumbnail with 60 alternating black and white vertical stripes and held it at arm's length, each stripe would be about one arcminute wide.) Because Venus is closer to the sun and to Earth, its surface reflects significantly more photons into your eyes than does Jupiter's, causing greater entoptic glare.

But a second contributor is also in play in the irradiation illusion. Glare could not explain, for example, the fact that Galilean moons appear smaller when seen as black dots against Jupiter's mass than when seen as white beacons against the night sky. The answer, von Helmholtz realized, must reside in how the brain processes light versus dark objects. Scientists are only now finding ways to elucidate these neural processes.

As the examples in this column illustrate, the interplay between light and dark is critical not only to stargazing but to our everyday vision because contrast is fundamental to how we see everything. M

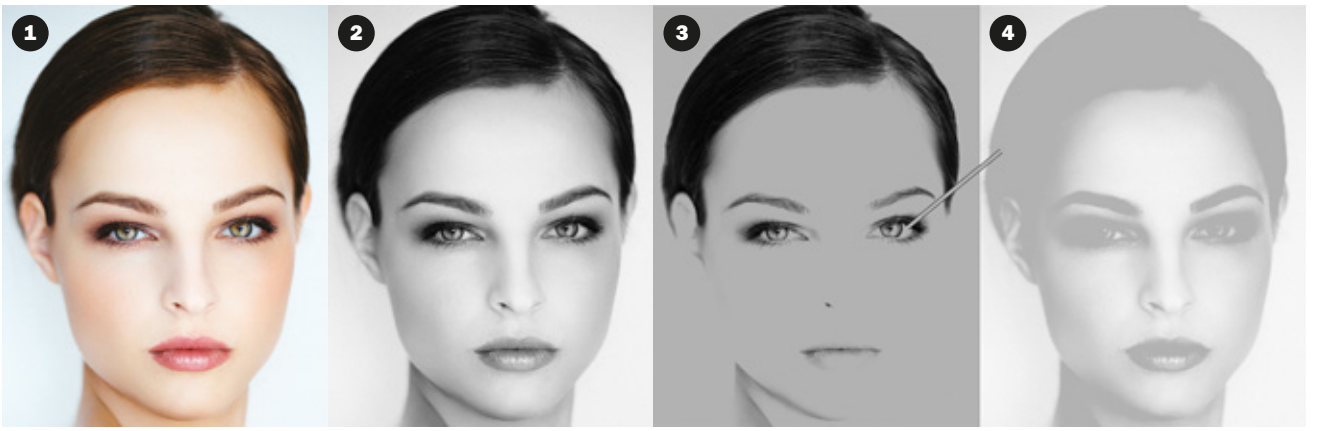
BY STEPHEN L. MACKNIK AND SUSANA MARTINEZ-CONDE

Stephen L. Macknik and Susana Martinez-Conde are professors of ophthalmology at SUNY Downstate Medical Center in Brooklyn, N.Y. They are authors of the Prisma Prize–winning *Sleights of Mind,* with Sandra Blakeslee (http://sleightsofmind.com).

Send suggestions for column topics to **MindEditors@sciam.com**

WANG LETIAN www.luckwlt.com; SEAN McCABE (*Macknik* and *Martinez-Conde*)

CONTRAST VS. DETAIL

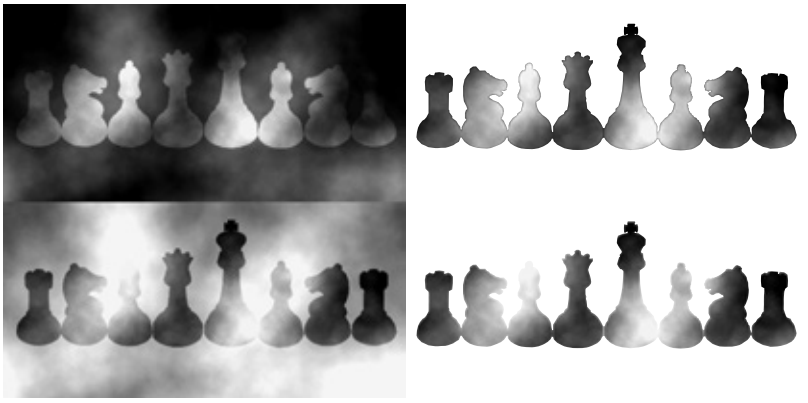


New discoveries help to show how neural processing in the visual system results in light objects looking larger than dark objects. These findings—from the laboratories of Jose-Manuel Alonso of the State University of New York College of Optometry and David Fitzpatrick of the Max Planck Florida Institute for Neuroscience—explain not only much of Galileo's puzzling observations but also the ways we experience contrast itself.

The series of face images here, by Alonso, demonstrate how light versus dark processing plays out in our everyday vision. In image 1, we have a normal color photograph. In image 2, we see it in gray scale. Interesting things start to happen if we view solely the pixels that are dark in the image (less than the median brightness of the image) versus those that are light (the brighter 50 percent of the pixels).

Notice how sharp and precise the dark-pixels version is (*3*). This observation follows from the discovery that the neural system that processes darks does so with high resolution and precise spatial detail. In the light-pixels image (*4*), the perception of contrast is strong, but detail is lost. Alonso's illusion won placement as a top-10 finalist in the 2016 Best Illusion of the Year Contest.

The researchers found that light-processing neurons receive input from larger areas of the visual scene (and therefore have lower resolution) than dark-processing neurons (which thus have higher resolution). In normal vision, the dark- and light-processing systems work together to create contrast, which gives rise to powerful effects. For example, the whites of the eyes in the dark-pixels image appear to be much lighter than the hair in the light-pixels image, and yet if we connect the two with a strip that matches their color, we can see that they are actually identical. (Remember: the lightest pixels in the dark image are the same shade as the darkest pixels in the light image—both equal the median brightness of the normal grayscale image.) This suggests that any difference in perceived detail or contrast must be caused by how the brain processes lights versus darks.



GETTY IMAGES (*woman*); JOSE-MANUEL ALONSO (*face series*); FROM "IMAGE SEGMENTATION AND LIGHTNESS PERCEPTION," BY BARTON L. ANDERSON AND JONATHAN WINAWER, IN *NATURE*, VOL. 434; MARCH 3, 2005 (*chess pieces*)

BLACK AND WHITE AS EQUIVALENT

Barton L. Anderson, now at the University of Sydney in Australia, and Jonathan Winawer, now at New York University, have pushed to the limit the remarkable fact that a gray surface can look light or dark depending on its context. The chess pieces above and below are identical, but the variations in the surrounding clouds make us perceive the upper pieces as white and the lower ones as black. Removing the cloudy background (*comparison at right*) eliminates the illusion. Checkmate!

MORE TO EXPLORE

- **Image Segmentation and Lightness Perception.** Barton L. Anderson and Jonathan Winawer in *Nature,* Vol. 434, pages 79–83; March 3, 2005.
- **Neuronal Nonlinearity Explains Greater Visual Spatial Resolution for Darks Than Lights.** Jens Kremkow et al. in *Proceedings of the National Academy of Sciences USA,* Vol. 111, No. 8, pages 3170–3175; February 25, 2014.
- **Topology of ON and OFF Inputs in Visual Cortex Enables an Invariant Columnar Architecture.** Kuo-Sheng Lee et al. in *Nature,* Vol. 533, pages 90–94; May 5, 2016.
- Jose-Manuel Alonso's top-10-finalist entry, 2016 Best Illusion of the Year Contest: **http://illusionoftheyear.com/2016/06/lights-and-darks-in-vision**

LEARNING

Why Math Education in the U.S. Doesn't Add Up

Research shows that an emphasis on memorization, rote procedures and speed impairs learning and achievement

By Jo Boaler and Pablo Zoido

In December the Program for International Student Assessment (PISA) will announce the latest results from the tests it administers every three years to hundreds of thousands of 15-year-olds around the world. In the last round, the U.S. posted average scores in reading and science but performed well below other developed nations in math, ranking 36 out of 65 countries.

We do not expect this year's results to be much different. Our nation's scores have been consistently lackluster. Fortunately, though, the 2012 exam collected a unique set of data on how the world's students think about math. The insights from that study, combined with important new findings in brain science, reveal a clear strategy to help the U.S. catch up.

The PISA 2012 assessment questioned not only students' knowledge of mathematics but also their approach to the subject, and their responses reflected three distinct learning styles. Some students relied predominantly on memorization. They indicated that they grasp new topics in math by repeating problems over and over and trying to learn methods "by heart." Other students tackled new concepts more thoughtfully, saying they tried to relate them to those they already had mastered. A third group followed a so-called self-monitoring approach: they routinely evaluated their own understanding and focused their attention on concepts they had not yet learned.

In every country, the memorizers turned out to be the lowest achievers, and countries with high numbers of them—the U.S. was in the top third—also had the highest proportion of teens doing poorly on the PISA math assessment. Further analysis showed that memorizers were approximately half a year behind students who used relational and self-monitoring strategies. In no country were memorizers in the highest-achieving group, and in some high-achieving economies, the differences between memorizers and other students were substantial. In France and Japan, for example, pupils who combined self-monitoring and relational strategies outscored students using memorization by more than a year's worth of schooling.

The U.S. actually had more memorizers than South Korea, long thought to be the paradigm of rote learning. Why? Because American schools routinely present mathematics procedurally, as sets of steps to memorize and apply. Many teachers, faced with long lists of content to cover to satisfy state and federal requirements, worry that students do not have enough time to explore math topics in depth. Others simply teach as they were taught. And few have the opportunity to stay current with what research shows about how kids learn math best: as an open, conceptual, inquiry-based subject.

JO BOALER is a professor of mathematics education at Stanford University. **PABLO ZOIDO**, a former analyst at the Organization for Economic Co-operation and Development (OECD), is now an education lead specialist at the Inter-American Development Bank.

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SUHARU OGAWA

To help change that, we launched a new center at Stanford University in 2014, called Youcubed. Our central mission is to communicate evidence-based practices to teachers, other education professionals, parents and students. To that end, we have devised recommendations that take into consideration how our brains grapple with abstract mathematical concepts. We offer engaging lessons and tasks, along with a wide range of advice, including the importance of encouraging what is known as a growth mindset—offering messages such as "mistakes grow your brain" and "I believe you can learn anything."

The foundation all math students need is number sense—essentially a feel for numbers, with the agility to use them flexibly and creatively. A child with number sense might tackle 19 × 9 by first working with "friendlier numbers"—say, 20 × 9—and then subtracting 9. Students without number sense could arrive at the answer only by using an algorithm. To build number sense, students need the opportunity to approach numbers in different ways, to see and use numbers visually, and to play around with different strategies for combining them. Unfortunately, most elementary classrooms ask students to memorize times tables and other number facts, often under time pressure, which research shows can seed math anxiety. It can actually hinder the development of number sense.

In 2005 psychologist Margarete Delazer of Medical University of Innsbruck in Austria and her colleagues took functional MRI scans of students learning math facts in two ways: some were encouraged to memorize and others to work those facts out, considering various strategies. The scans revealed that these two approaches involved completely different brain pathways. The study also found that the subjects who did not memorize learned their math facts more securely and were more adept at applying them. Memorizing some mathematics is useful, but the researchers' conclusions were clear: an automatic command of times tables or other facts should be reached through "understanding of the underlying numerical relations."

Additional evidence tells us that students gain a deeper understanding of math when they approach it visually—for instance, seeing multiplication facts as rectangular arrays or quadratic functions as growing patterns. When we think about or use symbols and numbers, we use different brain pathways than when we visualize or estimate with numbers. In a 2012 imaging study, psychologist Joonkoo Park, now at the University of Massachusetts Amherst, and his colleagues demonstrated that people who were particularly adept at subtraction—considered conceptually more difficult than addition—tapped more than one brain pathway to solve problems. And a year later Park and psychologist Elizabeth Brannon, both then at Duke University, found that students could boost their math proficiency through training that engaged the approximate number system, a cognitive system that helps us estimate quantities.

Brain research has elucidated another practice that keeps many children from succeeding in math. Most mathematics classrooms in the U.S. equate skill with speed, valuing fast recall and testing even the youngest children against the clock. But studies show that kids manipulate math facts in their working memory—an area of the brain that can go off-line when they experience stress. Timed tests impair working memory in students of all backgrounds and achievement levels, and they contribute to math anxiety, especially among girls. By some estimates, as many as a third of all students, starting as young as age five, suffer from math anxiety.

The irony of the emphasis on speed is that some of our world's leading mathematicians are not fast at math. Laurent Schwartz—who won math's highest award, the Fields medal, in 1950—wrote in his autobiography that he was a slow thinker in math, who believed he was "stupid" until he realized that "what is important is to deeply understand things and their relations to each other. This is where intelligence lies. The fact of being quick or slow isn't really relevant."

A number of leading mathematicians, such as Conrad Wolfram and Steven Strogatz, have argued strongly that math is misrepresented in most classrooms. Too many slow, deep math thinkers are turned away from the subject early on by timed tests and procedural teaching. But if American classrooms begin to present the subject as one of open, visual, creative inquiry, accompanied by growth-mindset messages, more students will engage with math's real beauty. PISA scores would rise, and, more important, our society could better tap the unlimited mathematical potential of our children. M

THE PRESSURE OF TIMED TESTS IMPAIRS WORKING MEMORY—AND IT CONTRIBUTES TO MATH ANXIETY, ESPECIALLY AMONG GIRLS.

MORE TO EXPLORE

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- **Training the Approximate Number System Improves Math Proficiency.** Joonkoo Park and Elizabeth M. Brannon in *Psychological Science,* Vol. 24, No. 10, pages 2013–2019; October 2013.
- **Mathematical Mindsets: Unleashing Students' Potential through Creative Math, Inspiring Messages and Innovative Teaching.** Jo Boaler. Wiley, 2015.

"It was literally true: I was going through life asleep. My body had no more feeling than a drowned corpse. My very existence, my life in the world, seemed like a hallucination. A strong wind would make me think my body was about to be blown to the end of the earth, to some land I had never seen or heard of, where my mind and body would separate forever."

—From *Sleep*, by Haruki Murakami, 1989

JON HAN (*illustration*); SEAN McCABE (*Koch*)

PHYSIOLOGY

Sleeping While Awake

During microsleep, the entire brain nods off so briefly that we often don't notice it. Now research shows that individual neurons in the brain can slumber, too, especially when we are sleep-deprived

BY CHRISTOF KOCH

Christof Koch is president and chief scientific officer at the Allen Institute for Brain Science in Seattle. He serves on *Scientific American Mind*'s board of advisers.

We've all been there. You go to bed, close your eyes, blanket your mind and wait for consciousness to fade. A timeless interval later, you wake up, refreshed and ready to face the challenges of a new day (note how you can never catch yourself in the act of losing consciousness!). But sometimes your inner world does not turn off—your mind remains hypervigilant. You toss and turn but can't find the blessed relief of sleep. The reasons for sleeplessness may be many, but the consequences are always the same: You are fatigued the following day, you feel sleepy, you nap. Attention wanders, your reaction time slows, you have less cognitive-emotional control. Fortunately, fatigue is reversible and disappears after a night or two of solid sleep.

We spend about one third of our lives in a state of repose, defined by relative behavioral immobility and reduced responsiveness to external stimuli. Cumu-

latively, this amounts to several decades' worth of sleep over the lifetime of an average person. Ah, I know you're thinking, Wouldn't it be great if we cut down on this "wasted" time to be able to do more! When I was younger, I, too, lived by the motto "You can sleep when you're dead." But I've woken up to the fact that for optimal, long-term physical and mental health, we need sleep.

Humans share this need for daily sleep with all multicellular creatures, as anybody growing up with dogs, cats or other pets knows.

An understanding of sleep's importance can be observed by contemplating the biological process itself. Sleep is homeostatically regulated with exquisite precision: pressure to go to sleep builds up during the day until we feel sleepy in the evening, yawn continuously and nod off. If deprived of sleep, humans experience an ultimately irresistible need to seek repose—they, in fact, become "sleep drunk." An older, 19th-century term, closer to the truth, is "cerebral exhaustion," the brain demanding its rest.

In my last Consciousness Redux column, I described how clinicians define sleep by recording brain waves from a net of electroencephalogram (EEG) sensors placed on the scalp of the sleeper [*see photograph on next page*]. Like the surface of the sea, the electrical brain is ceaselessly in commotion, reflecting the unseen, tiny tremors in the cerebral cortex underneath the skull that are picked up by the EEG electrodes. Rapid eye movement (REM) sleep is characterized by low-voltage, choppy, swiftly changing brain waves (paradoxically, also typical of relaxed wakefulness), whereas non-REM sleep is marked by slowly rising and falling waves of larger amplitude. Indeed, the deeper and more restful the sleep, the slower and larger the waves that reflect the brain's idling, restorative activity. These voltage oscillations, referred to as delta waves, can be as slow as once every four seconds and as fast as four times a second (that is, in the 0.25- to four-hertz frequency range). Tuning into the discharge of individual neurons during deep sleep reveals discrete off periods, when nerve cells cease generating any electrical activity for 300 to 400 milliseconds. Such recurring silent periods, synchronized across large parts of the cortex, are the cellular hallmark of deep sleep.

Microsleep

My last column, "To Sleep with Half a Brain," highlighted the growing realization of sleep researchers that being awake and asleep are not all-or-none phenomena. Just because you're asleep doesn't necessarily imply that your entire brain is asleep. Conversely, as I will describe now, we have also learned that even when you're awake, your entire brain may not be awake.

A case in point for sleep intruding into wakefulness involves brief episodes of sleep known as microsleep. These intervals can occur during any monotonous task, whether driving long distances across the country, listening to a speaker droning on or attending yet another never-ending departmental meeting. You're drowsy, your eyes get droopy, the eyelids close, your head repeatedly nods up and down and then snaps up: your consciousness lapses.

In one experiment attempting to explore this condition, participants had to track a randomly moving target on a computer monitor with a joystick for 50 minutes. While straightforward, this visuomotor task demands nonstop attention that becomes difficult to sustain after a while. Indeed, on average, participants had 79 microsleep episodes per hour, lasting between 1.1 and 6.3 seconds apiece, with an attendant drop in performance. Microsleep shows up in the EEG record by a downward shift from activity dominated by the alpha band (8 to 13 Hz range) to oscillations in the theta band (4 to 7 Hz).

MICROSLEEP CAN BE FATAL WHEN DRIVING OR OPERATING MACHINERY SUCH AS TRAINS OR **AIRPLANES, HOUR AFTER TEDIOUS HOUR.**

Perniciously, subjects typically believe themselves to be alert all the time during microsleep without recalling any period of unconsciousness. This misapprehension can be perilous to someone in the driver's seat. Microsleep can be fatal when driving or operating machinery such as trains or airplanes, hour after tedious hour. During a microsleep episode, the entire brain briefly falls asleep, raising the question of whether bits and pieces of the brain can go to sleep by themselves, without the entire organ succumbing to slumber.

Indeed, Italian-born neuroscientists Chiara Cirelli and Giulio Tononi, who study sleep and consciousness at the University of Wisconsin–Madison, discovered "sleepy neurons" in experimental animals that showed no behavioral manifestation of sleep. In this research, 11 adult rats had microwires implanted into their frontal motor cortex, which controls movement. Inserted into the cortical tissue, the sensors picked up both the voltage called the local field potential (LFP), akin to the EEG, in addition to the spiking activity of nearby nerve cells. As expected, when awake, the LFP was dominated by low-amplitude, fast waves readily distinguishable from the larger and slower waves characteristic of non-REM deep sleep [*see box on page 23*].

The author, his head clad in a dense net of EEG sensors, participates in a sleep study in the laboratory of Chiara Cirelli and Giulio Tononi at the University of Wisconsin–Madison.

At the level of individual neurons, the awake animals' cortical cells chatted away in an irregular, staccato manner over an extended period. Conversely, during deep sleep, cortical neurons experienced pronounced "on" periods of neural activity and "off" times during which they are silent. This neuronal reticence occurs simultaneously all over the cortex. It alternates with regular on periods, leading to the rising and falling brain waves that are the hallmark of deep sleep.

Knowing all this, the researchers decided to probe further. Instead of letting the rats go to sleep at their usual bedtime, the experimentalists engaged the animals in a rodent version of late-night video gaming, continuously exposing them to toys and other objects to sniff, explore and play with. They tapped on the cage and otherwise prevented them from assuming a sleep posture or becoming drowsy. After four hours of such excitement, the rats could finally slumber.

As expected from previous animal and human studies, by the end of the sleep deprivation phase, the LFP began to shift to lower frequencies, compatible with the idea that the pressure for the animals to sleep steadily built up. Closer inspection of the electrical signatures, however, revealed something unexpected: occasional, sporadic, silent periods of all or most of the neurons in the recorded brain region [*see box on opposite page*] without the animals showing either behavioral or EEG manifestations of microsleep. These short, off-like episodes were often associated with slow waves in the LFP. The opposite happened during recovery sleep, toward the end of this six-hour period, when the pressure to sleep had presumably abated. At this point, large and slow waves in the LFP became more infrequent, and neuronal activity turned more irregular, as it did during wakefulness.

It appears that when awake but sleep-deprived, neurons show signs of sleepiness, whereas after hours of solid sleep, individual neurons start waking up. Careful statistical analysis confirmed these trends: the number of off periods increased during the four hours the rats were forced to stay awake, and the opposite dynamic occurred during recovery sleep.

One question was whether any one neuron fell asleep independent of any other neuron. Or was this occurrence more of a global phenomenon, whereby all neurons simultaneously transition to an off period? The answer, obtained by implanting a second array of microwires into a second cortical region—the parietal cortex, a quite distinct region from the motor cortex—was "yes" to both questions.

That is, sometimes neurons in both regions went off together, whereas at other times they did so independently. Yet as the sleep pressure built up, after several hours of being kept awake, neuronal activity during sleep deprivation did become more globally synchronized (as it does in deep sleep). Likewise, the longer the animal slept during the recovery period, the less likely slow waves were simultaneously detected at both cortical sites. Groups of neurons can be more easily recruited to produce the slow oscillations that constitute deep sleep when sleep pressure is high.

These results paint a more nuanced view of wakefulness and sleep than the prevailing one, in which both conditions were considered to be global, all-or-none states of consciousness. Instead these data, buttressed by single-neuron recordings from patients with implanted microelectrodes, as used occasionally in epilepsy treatment, suggest that even when the subject is awake, the individual's neurons can become tired and occasionally check out. The heavier the sleep pressure, the more likely this will happen simultaneously at many places in cortex. Conversely, after many hours of restful sleep, some of these neurons become de-

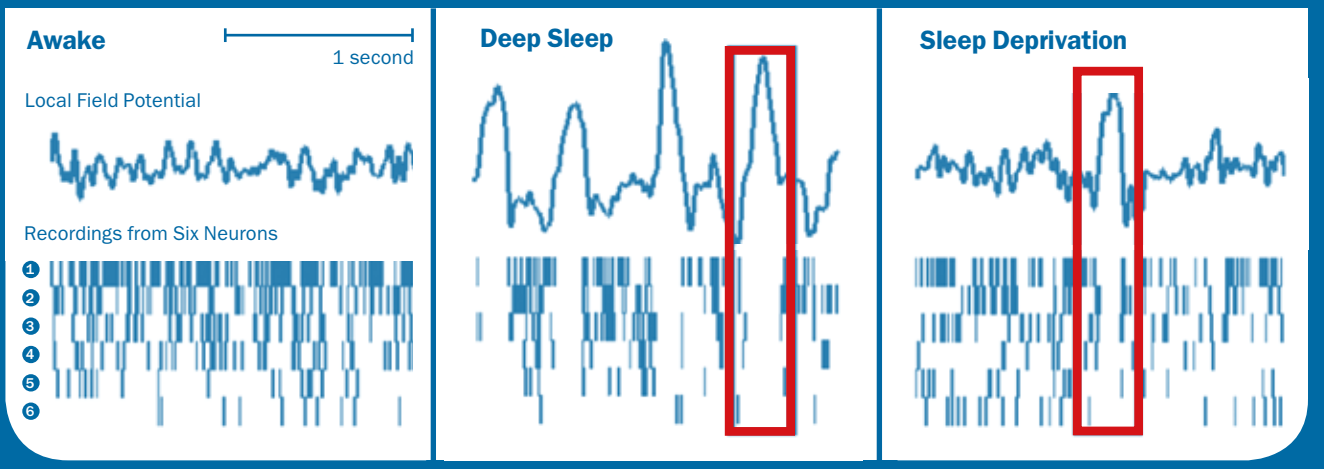
WHEN SLEEP-DEPRIVED, NEURONS CAN BECOME TIRED AND DISENGAGED, A MICROCOSM OF **WHAT HAPPENS TO THE WHOLE ORGANISM.**

COURTESY OF CHRISTOF KOCH

Partially Asleep

Brain studies in animals back the notion that a person could be partially asleep on the job after a late night, with no outward signs of weariness. Local field potential measurements—summed electrical activity of large populations of nerve cells—show fast, low peaks present when an animal is awake (*left panel*) and slower, wider waves (*center*) during deep non-REM sleep (also called slow-wave sleep). But when an animal is coaxed to stay awake past its bedtime, parts of its brain can go to sleep (local sleep), with occasional sharp peaks in neural activity akin to those registered during deep sleep (*right panel*).

The tick marks at the bottom show the activity of six closely spaced neurons—all of which periodically switch off during slow-wave sleep. The red boxes highlight the similarity between non-REM and local sleep.



FROM "LOCAL SLEEP IN AWAKE RATS," BY VLADYSLAV V. VYAZOVSKIY ET AL., IN *NATURE*, VOL. 472; APRIL 28, 2011

coupled from these brain-wide oscillations and begin to wake up.

But with neurons going off-line during sleep deprivation, shouldn't there be some deterioration in performance? After all, these neurons must serve some purpose, and if they drowse, something ought to suffer. To investigate this question, Cirelli, Tononi and their collaborators trained the rats to reach with one of their front paws through a narrow opening to grasp a sugar pellet on a shelf. If done clumsily, the pellet falls off and cannot be retrieved anymore.

Learning this task engages a particular sector of the motor cortex that undergoes change as a consequence of training. Trawling for off periods while the animal reaches out for the sweets, the investigators found these gaps in neuronal firing are more likely to occur in the motor cortex a fraction of a second before a failed attempt to grab the pellet as compared with when the rat successfully picked up a sweet treat. Indeed, the occurrence of a single off period lowered the odds of a successful trial by more than a third. These effects were restricted to the motor cortex and were not seen in the parietal cortex, which is not engaged by the reaching task. As the animals became more sleep-deprived, their overall performance suffered, as is typical for sleep-deprived humans.

Local Slumber

What this study discovered is the existence of local sleep during sleep deprivation: isolated cortical groups of neurons that briefly go off-line while the animal, to all outward appearances, continues to move about and do what it does. Local shut-eye is more likely to occur if those neurons are actively engaged, as they are when learning to grab a sugar pellet. Neurons, too, become tired and disengaged, a microcosm of what happens to the whole organism.

Extrapolating from these data, it seems plausible that as the pressure for sleep increases, the frequency of these off events and their preponderance in the cortex increase until activity in the entire brain becomes suddenly but briefly synchronized and the brain falls into deep sleep—the eyes close, and the head nods. The subject enters microsleep.

Sleep is a fascinating subject, even though we cannot knowingly experience deep sleep, because our consciousness is switched off. Sleep is a finely regulated aspect of our brain's daily cycle as the sun rises and sets, a state whose function remains controversial.

Over the past century clinicians and neuroscientists have discovered different sleep phases (rapid eye and nonrapid eye movements) and the distinct regions of the midbrain and brain stem involved in controlling them. What is more, these researchers have demystified narcolepsy, when patients abruptly and irresistibly fall asleep, microsleep and now local sleep. What will come next? M

MORE TO EXPLORE

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"You've got to be kidding me, Doc. I can barely keep my eyes open as it is, and you want me to pull an all-nighter?"

I smiled. "Yes, exactly that. Maybe even two or three."

ILLUSTRATIONS BY KAROLIS STRAUTNIEKAS

Sleep No More

Insomnia is a common symptom of major depression, and yet sleep deprivation can be part of the solution for a patient seeking quick relief

By Louisa J. Steinberg

It started out benignly enough. Jodi* had been feeling more stressed between meeting the growing demands of her high-stakes job in business management and shouldering more chores while her husband was away on business trips. Strapped for time, she started neglecting her usual self-care routines—eating healthy, exercising, taking time to relax. Not surprisingly, her mood was poor.

Things soon grew worse. She no longer enjoyed activities that were usually the highlight of her day: story time with her children, chatting on the phone with her mom, reading a book. Although she was constantly exhausted, she could not get a good night's sleep; she would toss and turn and still feel tired even when she

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Send suggestions for column topics to **MindEditors@sciam.com**

**Not the patient's real name.*

MAJOR DEPRESSIVE DISORDER

Diagnosis is based on the presence of five or more of these symptoms nearly every day over a two-week period:

1. Depressed mood most of the day*
2. Markedly reduced interest or pleasure in activities*
3. Significant weight loss or change in appetite
4. Insomnia or sleeping too much
5. Visible restlessness or sluggishness
6. Fatigue or loss of energy
7. Feelings of worthlessness or guilt
8. Poor concentration or ability to make decisions
9. Recurrent thoughts of death or suicide

**At least one of these is required for diagnosis.*
Adapted from the DSM-5.

slept in. Her performance at work had also been suffering; she began missing days because she just couldn't get out of bed.

Jodi knows she should have recognized these warning signs sooner. She had experienced major depression twice before, once in college and again in her late 20s after a breakup. Now in her late 30s, she had been off antidepressants for years. Yet she found herself back in that dark place, barely eating and unable to concentrate enough to read even a short paragraph. Her thoughts circled around the same unpleasant memories and nagging fears. She felt hopeless and guilty.

When she came to see me, I confirmed what Jodi already suspected: she had relapsed into a major depressive episode. Thankfully, she was not having thoughts of hurting herself, and because she had good support from her family and friends, she would not need to be hospitalized. I recommended that she start on an antidepressant immediately. Jodi agreed but was disappointed to learn it might be anywhere from four to six weeks before her medication took effect. She had already fallen behind on work, the holidays were coming up, and she did not want to put her life on hold for this depression any longer. "Isn't there something that will work faster?" she lamented.

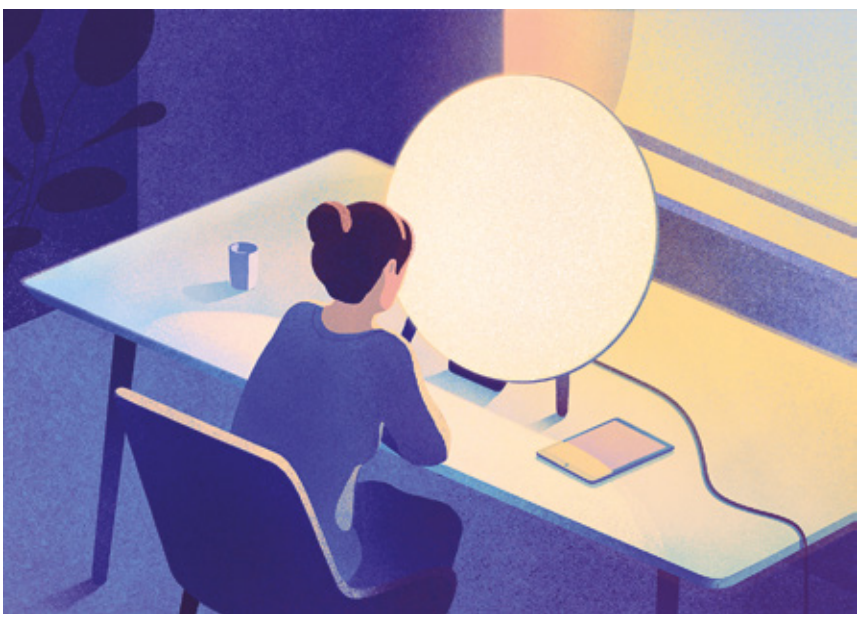
"Well, there is one strategy we could try," I said. "How do you feel about skipping a few nights of sleep?"

Jodi's jaw dropped. "You've got to be kidding me, Doc. I can barely keep my eyes open as it is, and you want me to pull an all-nighter?"

I smiled. "Yes, exactly that. Maybe even two or three."

Standard antidepressant therapies are often effective in treating depression, but it takes time for them to work. In recent years research has focused on trying to find treatments that could improve symptoms within days as opposed to weeks. Although it seems counterintuitive, an old and often forgotten approach to improving mood rapidly involves short-term sleep deprivation. As a 2015 review in *Current Psychiatry Reports* noted, therapies that manipulate sleep can significantly improve depressive symptoms. The treatment is not for everyone—elderly patients and those with cognitive impairment, for instance, would not be good candidates—nor should people try it without a clinician's guidance. Still, it can help bring relief before medication kicks in.

Sleep issues are a core symptom of depression. They exacerbate fatigue and cognitive deficits, which are also core symptoms, making daily functioning even more challenging. People often cope by taking daytime naps, which makes falling asleep at night difficult, feeding the cycle of sleep dysregulation. These



observations have led many researchers to ask what the connection between sleep and mood is and what biological determinants underlie this relation.

All creatures sleep—or at least exhibit a circadian rhythm based on the earth's light-dark cycle. In animals, populations of nerve cells have rhythmic activity thought to be the basis of an internally generated timekeeper. This master clock can be found in the brain's suprachiasmatic nucleus. If this area is damaged, daily bodily rhythms become erratic. Research has also shown that genetic regulation of circadian rhythms is off-kilter in people with major depression.

Circadian-sensitive circuits are influenced by external cues, the most important being sunlight. They receive information about the timing and duration of sunlight from the eye: a special subset of cells in the retina, found at the back of the eyeball, transmits this information, even in people who are blind.

Many of us have experienced the power of circadian misalignment when traveling to another time zone. The mismatch between the environmental light-dark cycle and that of our neural circadian pacemakers is more commonly referred to as jet lag. (We undergo this experience to a lesser degree twice a year during daylight saving time switches.) It can take several days for neural circuits to become entrained to the new light-dark schedule, but in the interim, sleep is disrupted, appetite does not match up with mealtimes and our state of mind can suffer.

But could adjusting these cycles reset our mood and, in turn, address mood disorders? In fact, it has been known for 200 years that sleep deprivation can treat depression rapidly. (In 1818 German psychiatrist Johann Christian August Heinroth described the therapy in his *Textbook of Disturbances of Mental Life*.) Since the 1960s numerous clinical studies have shown that as little as one night of sleep deprivation can relieve symptoms, and a 2015 paper reported swift improvement in 50 to 80 percent of subjects.

Sleep is generally thought to be a mood-stabilizing force. It is certainly one of the first symptoms targeted by clinicians, usually with medications, to help patients feel better. Furthermore, studies have shown that sleep deprivation has an effect on neurotransmitter activity throughout the brain, just like some medications. In 2015 scientists at the University Medical Center Freiburg in Germany, the University of Bonn in Germany, the University of Naples Federico II in Italy and the National Institutes of Health discovered that the effects of sleep deprivation, tricyclic antidepressants and ketamine on mood may all rely on the same molecular target, a receptor in the brain's frontal lobes whose activity may ultimately influence brain connectivity related to mood regulation.

Unfortunately, the gains made by sleep-deprivation therapy alone are not long-lasting. Typically depressive symptoms return within one week, which still leaves four to six weeks before antidepressants can kick in.

There may, however, be a way to maintain this therapy's benefits using the ultimate circadian rhythm calibrator: sunlight. In one of the earliest studies combining sleep and full-spectrum light therapies, psychiatrists at the University of Vienna asked 20 patients with depressive symptoms who had undergone sleep deprivation to take an antidepressant medication in conjunction with either dim or bright light exposure. Their findings, published in 1996, showed that among those patients who responded well to sleep deprivation, receiving daily bright light maintained the antidepressant effect of that limited sleep during a trial period of seven days.

My colleagues and I are now investigating whether this benefit can be maintained even longer. Thus, I offered Jodi the opportunity to participate in a new study of "wake therapy," which combines sleep deprivation, timed sleep (that is, following a schedule in which sleep time shifts over a number of days) and light therapy. She was hesitant—but then again, she was already sleeping poorly, so what did she have to lose?

To avoid workplace fatigue, Jodi started the treatment that weekend. Adhering to a schedule we had tailored for her, she went through a period of prolonged wakefulness, an "all-nighter." After that point, she followed a prescribed routine of specific bed and wake times to shift her sleeping cycle. She also sat in front of a full-spectrum light box at breakfast every morning.

When I saw Jodi the next week, she reported that although staying up had been tough, she had noticed a significant improvement in her symptoms. She no longer felt depressed, was able to go back to work and was handling the stresses of everyday life more successfully. We continued to work together, and within a few weeks, with the help of medications, wake therapy and psychotherapy, Jodi was herself again—just in time for the holidays. **M**

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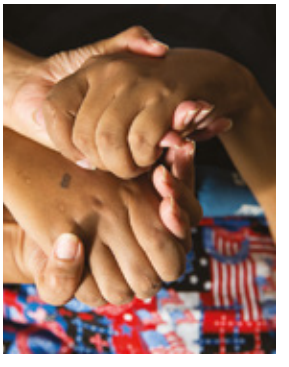
From Our Archives

- **Out of Sync.** Emily Laber-Warren; September/October 2015.

The Givers

Tens of millions of people tend to a loved one on a full- or part-time basis, often putting their own life on hold. Now researchers are finding ways to help them care for others without losing themselves

By Francine Russo



An explosion in Afghanistan nearly took Luis Alvarado's life—and forever changed that of his mother, Sonia, who is a pastor. Although their faith was tested, the experience taught the entire family both how to give and to receive care.

On November 14, 2011, Sonia Alvarado got a 5 A.M. call from the U.S. Army. Her son, Luis, had been injured by an improvised explosive device near Kandahar, Afghanistan. Sonia and her husband, Julio, both Methodist pastors, immediately flew to Germany, where their 24-year-old son lay in a hospital in a coma, tubes crisscrossing in and out of his body. The doctors told the parents to say good-bye; Luis was showing minimal brain activity. "You don't know how stubborn my son is," Sonia told them.

She and Julio sat beside Luis, talking unceasingly to him. Finally, they saw him shed tears. "Keep fighting," his mother begged, "and we will fight with you." Thinking back on that day, she says: "We made the decision right there that we will always be taking care of him."

Across the country, nearly one in five adults—about 43.5 million Americans—have stepped up to that kind of responsibility, providing care to loved ones who are sick, frail or disabled, according to a joint report from the AARP and the National Alliance for Caregiving. The vast majority (85 percent) are tending a relative: a parent or parent-in-law in nearly half of cases, a spouse or partner for another 12 percent, and the rest a mix of uncles, aunts, grandparents and others.

It is hard, relentless work and unpaid, although the economic value is huge—estimated at $470 billion in 2013. As one might expect, those who log long hours are especially likely to experience emotional and physical stress, negative health effects and financial strain. Compared with the general population, they are more apt to describe their health as "fair" or "poor," and nearly a quarter say that caregiving has led to deteriorating health.

As the population ages and caregivers' numbers mount ever higher, the emotional, physical and financial costs to individuals and society are ballooning. In 1993, under President Bill Clinton, the U.S. Congress passed the Family and Medical Leave Act, which offers eligible workers some relief in the form of protected leave from work to care for a family member. In recent years more than half of states have approved AARP-developed legislation that requires hospitals to provide training in essential medical tasks for those caring for a relative newly released from a hospital. Nevertheless, the U.S. continues to lag behind many European and some Asian countries when it comes to support for caregivers.

It is not as if we do not know how to help. For decades—as longevity and the demand for caregiving have skyrocketed—social scientists have been unraveling the question of why some people fare well as caregivers where others struggle. In the process they have identified specific strategies that can help caretakers manage the burdens and maximize the rewards of their role.

These scientists recognize that caregiver well-being depends on far more than meeting practical, medical and financial needs. Family caregiving is a profound and deeply personal experience. It touches on our mortality and vulnerability, who we are as humans, as sons and daughters, husbands, wives, fathers and mothers. It asks us to find meaning in loss and satisfaction in what many would see as drudgery or endless self-sacrifice. Fundamentally, how we think about the role of caregiving plays a powerful part in whether we buckle under the strain of that position or derive a sense of purpose and fulfillment.

FAST FACTS

CAREGIVING: LIGHTENING THE LOAD

1. There are an estimated 43.5 million unpaid caregivers in the U.S. Most are tending a relative, and nearly a quarter report that their health has suffered under the strain.
2. Scientists have found that culture, gender and relationship dynamics can help explain why some people fare better than others when caring for someone in need.
3. Respite programs, counselors, peer-support groups and interventions can all help caregivers manage the challenges of their role.

Gender, Culture, Community

People can think of tending to a loved one as a trial or a blessing. In practice, it is a combination of both—and many different factors can tip the scales. Steven H. Zarit, a pioneering gerontologist and distinguished professor emeritus at Pennsylvania State University, is among the most devoted to this puzzle. He co-created the Zarit Burden Interview, now an internationally used tool in caregiving, to assess its emotional, physical and social impact on individuals. According to Zarit, the perception of burden is subjective and depends more on the individual's beliefs, relationships and culture than on the weight of day-to-day duties. "Some people caring for those with many dis-

PRECEDING PAGES AND OPPOSITE PAGE: BUFF STRICKLAND

Luis, who uses facial expressions and his hands to communicate, is aided by his entire family: (*from far left*) parents Sonia and Julio Alvarado; sister Mariana Stovall and her children Meelo, Amaya and Alejandra.

ruptive problems feel little burden. Others feel overwhelmed," he says.

The relationship between "care partners," the current term for caregiver and care recipient, matters a great deal, as does the quality of that relationship: loving, hostile or ambivalent. Greater emotional closeness between spouse/spouse or child/parent partners, for example, often benefits the care recipient. But a 2012 study of dementia caregivers by Utah State University gerontologist Elizabeth B. Fauth and her colleagues found that for the caregiver, the experience was mixed. According to Fauth, it combined positive experiences with an increasing sense of loss, yearning and, for some, depression.

In a 2013 study, New York psychotherapist Judy R. Strauss reported a difference between caregivers who were sons and daughters versus those who were children-in-law (primarily women). The adult children suffered poorer mental health and family strain, whereas sons and daughters by marriage reported less family strain and more support from their spouse. This pattern may reflect a number of factors. People may offer more praise and support to children-in-law while taking a biological child's caregiving for granted; kids may feel more pressured to tend to their own parents than someone else's; and finally, it may be less emotionally draining and painful to watch an in-law's deterioration than a parent's.

Gender differences hint at similar issues. Women caregivers, as a group, have been found over and over to fare worse than men—and wives worst of all. In a 2014 study of 533 caregivers reported in the *Journal of Family Nursing*, for example, the researchers documented that men generally feel less burden than women. On the whole, people see caregiving as a woman's duty. Therefore, females tending to a loved one are conforming to expectations, but males are acting "against type" and may receive more appreciation. Other studies have found the belief that caregiving is women's work contributes to female reluctance to use care services, so when they do enlist outside help, they feel less control and satisfaction than men in the same circumstances. Men are therefore better at asking for help and can receive support without feeling they have failed or been "displaced" by paid service providers such as adult day care workers or home health aides.

Finally, culture and ethnicity play a role. Several studies have confirmed Peggye Dilworth-Anderson's 2004 finding

Caregiving is hard, relentless work and unpaid—yet the economic value is estimated at more than $470 billion annually.

that, as a group, African-Americans caring for loved ones with dementia have a more positive experience than whites do, reporting less depression, stress and strain. Certain cultural values, she found, foster greater resilience and "active" coping styles. (People who actively cope tackle challenges head-on rather than avoiding them.) A 2015 study by Johns Hopkins University gerontologist David Roth found that Hispanics also experienced more of the positive side of caregiving than whites. "It may be because of their stronger family connections," says Roth, which result in more social support.

Many lessons can be drawn from such studies of group differences. Women, for example, may be taught to take a cue from men and relinquish the belief that they are the "default" care figure—and instead see their role as a choice and one for which they *should* seek support. Research on cultural differences suggests that all caregivers—whatever their race or ethnicity—would benefit from greater social support at the community level. These elements influence the meaning caregivers assign their role—a worthwhile, even ennobling endeavor or a thankless chore thrust on them by circumstances. Research has shown, Zarit says, that if people feel they are getting something positive out of the experience—pleasant moments together, a sense that their task is valued—they feel less stress.

The Best Case in a Worst-Case Scenario

When Luis Alvarado was transferred to San Antonio, he was a double amputee with brain injuries and was unable to speak or swallow. Today he functions with a feeding tube and colostomy and communicates with his hands and facial expressions.

In 2013 Luis's parents moved to San Antonio to care for their son 24/7. His sister, Mariana Stovall, and her husband and daughters joined them two years later. The entire family's faith was sorely tested. "We went through the process of grief," Sonia says, "being angry with God, the army, the government, everyone. Then we reached acceptance." She let go of other dreams and ambitions without regrets. "To care for our son is our life now," she says. "We don't know how long we'll have him with us. We all feel so good to be able to do this."

Friends and members of their close-knit church community lend a hand, bringing food and stepping in when Luis's immediate family gets sick. Throughout her life Sonia believed that people had a duty to serve others, but she had always been the giver. Her friends and congregants persuaded her to receive, explaining that it was good for *them* to give. "Now I *welcome* help," she says.

The Alvarado family was especially well positioned to succeed as caregivers. As Latinos and Methodists, their culture and faith gave their sacrifices meaning. They felt they had the necessary strength and competence to learn and perform the required nursing tasks at a high level. And they were a close and highly functional family before the tragedy hit them.

Sex and culture can make a powerful difference. Women caregivers, as a group, tend to fare worse than men.

They also demonstrate a quartet of factors proven to improve the odds of coping well as caregivers. In 1990 the late sociologist Leonard Pearlin identified three key psychological elements of caregiving: mastery (that is, a sense of control of our lives), social support and coping strategies. Scientists have recently added a fourth: strategies that directly reduce the caregiver's physical stress levels. In practice, there is a dynamic interplay among these factors. Improve a caregiver's ability to manage difficult symptoms, and you improve the person's sense of mastery. Foster the caregiver's ability to care for himself or herself, and you reduce stress levels and bolster the capacity to care well, perhaps more lovingly or, at least, more patiently.

Strategies for Coping

Care partners know each other far better than a doctor and patient. Yet a caregiver often lacks the knowledge that is needed to handle frightening or irritating symptoms—let alone maintain some sense of mastery when a condition worsens. Dementia caregivers, for instance, often have to confront a loved one's agitation, sleeplessness, wandering and incontinence.

Solutions are invariably tailored to specific illnesses, but many strategies are adaptable across diseases. "One key for caregivers," Roth says, "is not to take the behaviors personally." A wife, for example, whose spouse has dementia might learn to see her husband's tirade not as a sign of disrespect but an indication that he is frustrated with his lost capacity to do routine tasks. Roth has shown that it is possible to teach this kind of reappraisal.

In a 2004 study, Roth and his colleagues assigned 406 caregivers of a spouse with Alzheimer's disease to receive either standard care or a counseling and support program aimed at reducing negative reactions to behavior problems. Four years later, although the frequency of problematic behaviors did not lessen, the counseled caregivers were significantly less likely to react negative-

THE AUTHOR

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Caregivers: A Portrait in Numbers

ILLUSTRATIONS BY PETER HOEY

WHO ARE THEY?

Estimated Total in the U.S.

43.5 million

Gender

At least 60% are female

Race & Ethnicity

- Hispanic adults report the highest prevalence of caregiving responsibilities: 21% care for a loved one vs. 20.3% of African-Americans, 19.7% of Asian-Americans and 16.9% of whites

WHO THEY TEND AND WHAT THEY DO

- Nearly 50% of those caring for adults do so for a parent or parent-in-law
- 12% tend a spouse or partner
- 15% care for a nonfamily member
- Female caregivers are more likely to provide personal care: 36% help with dressing and 31% with bathing vs. 24% and 17% for men

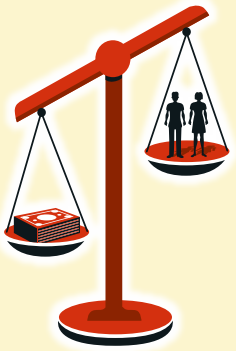
HOW MUCH TIME DO THEY DEVOTE?

Weekly Hours

Family caregivers spend an average of 24.4 hours per week, but nearly 1 in 4 spends 41 hours or more providing care

Duration

The average length of a caregiver's role is 4 years. 50% of caregivers provide care for a year or less, and 24% provide care for 5 years or more



COSTS & BENEFITS

Work/Income

- Women give up an estimated $324,000 in earnings on average; men lose $284,000
- Female caregivers are more likely to stop working (12% vs. 3% for men) or take a less demanding job (16% vs. 6%)
- Single women caring for their family members are 2.5 times more likely than noncaregivers to live in poverty in old age

Health

- 72% of family caregivers report not going to the doctor as often as they should, and 55% say they skip doctor appointments for themselves
- 63% report poor eating habits
- 58% say they exercise less than before taking on caregiving
- 40% to 70% have clinically significant symptoms of depression; a quarter to half of this group meet the diagnostic criteria for major depression

Rewards

- 81% of those caring for dementia patients reported "gains" as well as "strains." The main benefits: spiritual growth, personal growth, feelings of mastery and accomplishment

WHAT DO THEY NEED?

Assistance

84% of caregivers say they need more help and better information; one third say they have no help, paid or unpaid

Biggest Worries

- Keeping their loved one safe (42%)
- Managing their own stress (42%)
- Making end-of-life decisions (22%)

ly (such as getting angry). This matters because studies have shown that caregivers' *subjective* evaluations of their main sources of stress were better predictors of how well they fared than the actual frequency of those stressors.

Another powerful strategy is to focus on boosting rewards. Classic research has found that if dementia caregivers list things their loved one used to enjoy or that they enjoyed together—walks in the park, eating ice cream, dancing to oldies—then do them again, both care partners experience an uplift and a reinforcement of their closeness. More recently, a pilot study by Stanford University research professor and psychologist Dolores Gallagher-Thompson and her colleagues found that in caregivers of people of different ages with intractable depression, shared, happy activities benefited the caregivers' well-being.

Gallagher-Thompson also co-authored a 2015 study with dementia caregivers that involved scheduling pleasant events and enhancing communication between care partners. The experiment found that the 29 caregivers who had this kind of "enhanced behavioral activation" added to a standard psychoedu-

Wendi Steines (*center*) with her sons, 11-year-old Adam (*left*) and 14-year-old Nicholas (*right*), both of whom have autism. She finds strength in focusing on gratitude and recalling her boys' achievements.

COLIN LENTON

cational program had decreased depression compared with a control group of 30 caregivers who had not been coached to schedule pleasant events with their care partners.

Managing Stress with Social Support

"The hardest part is getting myself to *breathe* some days," says Wendi Steines. At age 44, Steines is the divorced mother of 14-year-old Nicholas and 11-year-old Adam, both of whom have autism spectrum disorder, along with other behavioral syndromes. She has not participated in an organized intervention but has joined parent seminars and autism groups and has read widely, cobbling together her own self-help program composed of many of the elements tested in universities.

Part of her strategy is strong social support. Many interventions work to fortify this critical element. For example, counselors in the New York University Caregiver Intervention for Adult Children, designed to help people tending to parents with dementia, hold individual and family sessions that heighten support from a caregiver's social network—whether siblings, church members or old friends. In Steines's case, she developed her own strong moms' network in her local area, the New Jersey suburbs of Philadelphia. "We meet all the time, share a bottle of wine, laugh and babysit each other's kids," she says. The group helps her when she is sad and worried about her boys' futures and feeling overwhelmed by their symptoms.

Indeed, a British group led by psychologist Valerie Shilling of Brighton and Sussex Medical School carried out a qualitative study that put 12 parents, 23 "befrienders" (parents of a special-needs child trained to offer one-on-one emotional support to other parents), and 10 health care, social care and education service professionals in contact for one year. The study, published in 2015, found that shared experiences were central to how caretakers perceived peer support. The parents reported feeling greater emotional stability, personal growth and reduced isolation during the study. The befrienders also reaped benefits from their training, from mutual support and from the satisfaction of helping others.

Sometimes, however, caregivers must navigate their stressors alone. When, for example, Steines's "big sweetheart" Adam throws an hour-long fit over homework—screaming, flailing and kicking—she relies on behavioral strategies she has learned to increase the "up" moments with her boys and improve her own health, coping skills and happiness. Taking a deep breath and imagining her son's point of view, for example, helps her get through a difficult

moment. Such skills may be crucially important. A 2015 study by University of Wisconsin–Madison researcher Jieun Song and her colleagues, for example, found greater "cognitive aging" and memory problems among mothers in a sample of 128 midlife parents who had raised children with disabilities compared with 512 parents of children without disabilities. The investigators suspect that the difference was the result of "heightened parenting stress."

Adding targeted stress-reduction techniques such as meditation and mindfulness training to a program of behavior management is now showing particular promise both for parents like Steines and for caregivers of the elderly, according to several studies by Nirbhay N. Singh of Augusta University.

Technology may help. Although studies in this area are lacking, researchers such as Gallagher-Thompson encourage the use of smartphone apps to access guided meditation such as Calm and Headspace, as well as a series from British hypnotherapist Glenn Harrold. Steines makes use of these apps herself and reports that her boys like them, too.

Respite Can Refresh

Of the four critical characteristics of successful caregiving—mastery, coping skills, social support and reducing physical stress—the last is the latest to be studied. And researchers have recently proved that stepping away from caregiving on regularly scheduled mornings or days off can bring measurable relief.

Investigators of the Daily Stress and Health (DASH) study, led by Zarit, have tested this idea, with remarkable results. Zarit and his colleagues interviewed and tracked the hormone cortisol in 158 family caregivers of a person with dementia. They wanted to examine how the individuals' perceived and measured stress changed when they could take breaks from their duties by bringing their charges to a social adult day center for people with dementia.

The study, which was published in the *Gerontologist* this year, found that regular breaks for caretakers resulted in

Anatomy of an **Intervention**

Among the most successful approaches to helping caregivers is the New York University Caregiver Intervention (NYUCI), designed to support people tending to loved ones with dementia. The program was based on work in the late 1990s by N.Y.U. psychiatric epidemiologist Mary S. Mittelman. A key measure of its efficacy is the fact that caregivers in the program are able to successfully tend to their loved ones at home far longer than nonparticipants, delaying the need for institutionalization. Positive results from NYUCI have now been found in interventions in five states.

University of Minnesota gerontologist Joseph Gaugler and his colleagues have adapted NYUCI for adult children caring for parents. In 2013 they reported that just 37 percent of the adult-child caregivers who participated placed their parent in a facility versus 66 percent in the control group. Caregivers also reported better quality of life, reduced depressive symptoms and less stress in response to disruptive behaviors.

NYUCI is a multipronged program that includes referrals to support groups and mindfulness programs. The chief component is a series of individual and family therapy sessions targeted at problematic psychological dynamics within the caregiver and among family members. In addition to regularly scheduled sessions, participants can reach out for ad hoc counseling by telephone whenever they need it, whether Dad with dementia is screaming through the hallways at night or the caregiver's brother is accusing his beset sister of trying to "put Mom away." Across cultures, family dissension has long been shown to increase caregiver strain. A classic 1993 study found that for married caregiving daughters, siblings were both sources of support and stress. And a 2014 study of 90 dementia caregivers in Colombia found that negative family dynamics were significantly associated with caregiver depression and stress.

Sheryl Fairbanks, 65, of Roseville, Minn., participated in Gaugler's intervention in 2009. "I was caring 24/7 for four parents [her own and her husband's] in three houses with an assortment of ailments, including my mother's vascular dementia," she recalls. Fairbanks had recently left a long career as a successful IT executive. Her sister, she says briefly, was "not available" for caregiving or to attend family therapy sessions. Fairbanks's husband was her primary helper.

As part of the program, Fairbanks met for 90 minutes a month with family therapist Mark Reese, either at her home or at a nearby coffee shop. Reese helped her through diverse practical and emotional struggles over a period of 18 months. "Mark saved my life," she says of the experience that ended in May 2012, when the last parent died. Reese rescued her from depression, she says, by helping her see the big picture and find meaning and pride in her situation.

The success of this program has led, this past July, to the creation of N.Y.U.'s Alzheimer's Disease and Related Dementias Family Support Program, based in New York City. The state-funded program offers free counseling to caregivers in the area either in person, by videoconferencing or by telephone, depending on the caregiver's preference. Mittelman is currently recruiting caregivers from across the country to participate in a study to determine if the videoconferencing version can match the results of the original, in-person program. (For online information, go to http://bit.ly/NYU2c2g8.) If the remote intervention succeeds, it could reach many more people in need of support. ***—F.R.***

normal cortisol regulation on days of respite and better stress regulation overall, including higher levels of the antistress hormone DHEA-S the day after their break, even when on duty. The findings suggest that using adult day services for respite could improve caregivers' long-term health. Participants experienced less physiological stress on mornings before they took respite—perhaps because they were anticipating their next break.

Donald "Ed" Florida, a 77-year-old retired truck driver, was initially reluctant to take his wife, Ruth, to an adult day center after she was diagnosed with early Alzheimer's last year. He was afraid he would miss his spouse of 56 years. But his daughter endorsed the idea and suggested The Tender, a social day center for people with dementia in nearby Mount Laurel, N.J. After a few months, Ed began to appreciate the break and the time to get things done, especially as he took on more household tasks previously handled by Ruth, who is also 77. Meanwhile she can enjoy the social life, games and entertainment available at The Tender.

A 2013 Brigham Young University study of respite for couples with children on the autism spectrum also found impressive benefits. More respite care not only reduced daily stress but increased parents' caregiving uplifts and improved their marriages. Win, win, win.

Top Tips for Caregivers

Experts emphasize four key elements for managing the stress and maximizing the rewards of caregiving

Mastery: Learn as much as possible about the disorder you are dealing with. The more you know about typical symptoms and behaviors, the better you can anticipate problems and not take them personally—all of which helps to build a sense of competence and control.

Coping strategies: Turn to advocacy and support groups, counselors and therapists to learn specific skills such as how to develop a more positive view of a loved one's behavior and how to think about one's own journey as a caregiver. Learn to focus on good care for your relative rather than making the person happy, which is often an impossible job.

Social support: Set aside any notion that you should be able to handle the responsibilities on your own. Reach out to family, friends, religious organizations, volunteer organizations and illness-specific support groups for sympathy, for humor and for hands-on help.

Stress reduction: *Do* exercise and *do* use respite programs. Also, try mindfulness training. Although working with an expert in meditation is ideal, apps such as Calm and Headspace can be helpful.

To find specific guidance on all these fronts, call or check the Web sites for caregivers and disease advocacy organizations. These are among the best:

The Family Caregiver Alliance (www.caregiver.org) offers information and advice for every kind of caregiver.

National Alliance on Mental Illness (www.nami.org) lends support for caregivers of people with bipolar disorder, schizophrenia, depression and other mental illnesses.

Alzheimer's Association (www.alz.org) has local chapters providing education and support for every kind of dementia.

Autism Speaks (www.autismspeaks.org) provides resources to parents of children with autism and to autistic adults.

The Power of a Plan

The vast majority of caregivers experience "gains" as well as "strains" from the experience, which includes 81 percent of people caring for dementia patients, according to a 2005 study by University of Iowa professor of social work Sara Sanders. In her study, caregivers reported three kinds of benefit: spiritual growth and increased faith, personal growth, and feelings of mastery and accomplishment.

As researchers further investigate what makes these experiences rewarding, the lessons learned can benefit many, whether people have access to a specific program or not [*see box at left*]. By consulting experts or advocacy groups and gathering knowledge, they can, like Wendi Steines or the Alvarados, cobble together an informed approach to managing their responsibilities without losing themselves in their care for others.

The Support, Health, Activities, Resources and Education (SHARE) program, based at the Benjamin Rose Institute on Aging in Cleveland, offers some insight into how empowering planning ahead can be. Over the course of SHARE, counselors offer people with early-stage dementia and their caregivers five to six sessions in which the care partners learn about how the disease progresses, what decisions will need to be made at each point, and what support family, friends or professionals might provide.

Working together, the counselor and care partners develop a practical, written plan that the caregiver can refer to when the person with dementia can no longer adequately express preferences. This plan is a potent tool to relieve caregivers' feelings of guilt or inadequacy when they need additional help. Preliminary findings of controlled trials of SHARE, according to its principal investigator Carol Whitlatch, are that after counseling, caregivers take advantage of more services to help them cope. They also have a greater understanding of and better communication with their relative, compared with members of a control group who received a single information session. Although SHARE

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As his wife's Alzheimer's has progressed, Donald "Ed" Florida has taken on many of her chores. He has learned supportive strategies from caregivers at The Tender, a center for dementia patients that she attends.

The choice was not easy. "I'm so afraid of hurting my husband's pride," she says, "when he looks around and sees the other people who are there. Jim has led a life of the mind, and now he's losing that." She might not have been able to take this step had she and Jim not attended SHARE, at which point Jim insisted that he did not want to burden his loved ones. He wanted Nancy to accept help.

As his condition progresses, the Scotts will face more challenges. But by banding together as a family, making informed decisions, supporting each other and seeking help as needed, they can better weather what lies ahead. Making a plan for Jim has also helped Nancy to envision her own future. She recently became a grandmother and is setting aside time to enjoy her new granddaughter, Meredith. She also hopes to become involved in Alzheimer's advocacy. "I try to think about my life and how I'll do it," she says. "I want to come out the other side still vibrant and healthy." Given the new science from which she has benefited and the choices she has made thus far, her odds look good. **M**

was designed for dementia caregivers, Whitlatch says she has recently been awarded funding by the Retirement Research Foundation to adapt the program for other chronic conditions such as cardiovascular disease and diabetes.

Nancy and Jim Scott of Fairfax County, Virginia, participated in SHARE in 2015. The couple—she is a former teacher and he a retired public housing expert—have been married for 40 years and raised two daughters together. Today Jim, 78, is stricken with Alzheimer's, and Nancy, 69, has recently decided to make use of respite services, taking Jim to a center where he can socialize with other dementia patients.

MORE TO EXPLORE

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From Our Archives

- **When Character Crumbles.** Ingfei Chen; November/December 2010.

HOW WE MAKE SENSE OF TIME

LONG, SHORT, FORWARD AND BACK: OUR CONCEPTS OF TIME—AND HOW WE PROCESS IT IN THE BRAIN—ARE BASED ON OUR UNDERSTANDING OF PHYSICAL SPACE, WITH SOME SURPRISING CULTURAL VARIATIONS

By Kensy Cooperrider and Rafael Núñez

ILLUSTRATION BY BRATISLAV MILENKOVIC

"What is the difference between yesterday and tomorrow?"

The Yupno man we were interviewing, Danda, paused to consider his answer. A group of us sat on a hillside in the Yupno Valley, a remote nook high in the mountains of Papua New Guinea. Only days earlier we had arrived on a single-engine plane. After a steep hike from the grass airstrip, we found ourselves in the village of Gua, one of about 20 Yupno villages dotting the rugged terrain. We came all the way here because we are interested in *time*—in how Yupno people understand concepts such as past, present and future. Are these ideas universal, or are they products of our language, our culture and our environment?

As we interviewed Danda and others in the village, we listened to what they said about time, but we paid even closer attention to what they did with their hands as they spoke. Gestures can be revealing. Ask English speakers about the difference between yesterday and tomorrow, and they might thrust a hand over the shoulder when referring to the past and then forward when referring to the future. Such unreflective movements reveal a fundamental way

THE YUPNO CONCEPTION OF TIME IS NOT ANCHORED TO THE BODY, AS THE WESTERN ONE IS, BUT TO THE WORLD AND ITS CONTOURS.

of thinking in which the past is at our backs, something that we "leave behind," and the future is in front of us, something to "look forward" to. Would a Yupno speaker do the same?

Danda was making just the kinds of gestures we were hoping for. As he explained the Yupno word for "yesterday," his hand swept backward; as he mentioned "tomorrow," it leaped forward. We all sat looking up a steep slope toward a jagged ridge, but as the light faded, we changed the camera angle, spinning around so that we and Danda faced in the opposite direction, downhill. With our backs now to the ridge, we looked over the Yupno River meandering toward the Bismarck Sea. "Let's go over that one more time," we suggested.

Danda obliged, again using his hands to enliven his explanation. But as we expected, his gestures had changed. As he referred to "yesterday," he now gestured, not backward, but forward. As he explained "tomorrow," he gestured back over his shoulder, up toward the ridge [*see illustration at right*]. Inconsistent as these movements may seem, Danda was not confused. His gestures expressed the Yupno way of understanding time, one in which the future is not something in front of you—it is uphill. By having interviewees change sitting positions, we were able to show that it does not matter whether the slope is in front of you, behind you, to your left or to your right. The Yupno conception of time is not anchored to the body, as the Western one is, but to the world and its contours. By investigating cases such as these, we and other researchers are starting to piece together an answer to a question that has puzzled thinkers for centuries: How are human beings able to make sense of time?

Humans, like creatures ranging from amoebas and bees to mockingbirds and elephants, come with built-in equipment for perceiving some aspects of time, such as the rhythms of night and day, the waxing and waning of the moon, and the turning of the seasons. What separates humans from other animals is that we do not stop at merely sensing time's passage. We tackle time head-on—or at least we try. We dice it into units, even ones that go beyond what is perceivable, such as milliseconds, or that transcend our life span, such as millennia. We depict time graphically, talk about it ceaselessly and even make gestural models of it in the air as we talk. In short, humans everywhere create and rely on time concepts—ideas about the nature of time that allow us to make plans, follow recipes, share memories and discuss possible futures.

But what are our time concepts made of? What is going on in the mind of a speaker of Yupno, or English for that matter, when answering our question about the difference between yesterday and tomorrow? Recent research in cognitive science is uncovering a surprising answer. Across cultures, human time concepts depend, in large part, on metaphor—in particular, on what cognitive scientists call conceptual metaphor, in which we think about something, in this case time, in terms of something else, in this case space. Thus, we build our understanding of duration, of time's passage and of sequences of events out of familiar spatial ideas such as size, movement and location. The latest findings reveal that this basic "time is like space" metaphor appears to be universal around the world—yet it also takes strikingly different forms from one culture to the next.

A Yupno man produces contrasting gestures when talking about time. When he faces uphill (*1*), yesterday is behind him. When he faces downhill (*2*), yesterday is in front of him. His gestures for "tomorrow" (*3* and *4*) reflect the opposite pattern. These gestures express the Yupno way of thinking about the past as downhill and the future as uphill.

FROM "CONTOURS OF TIME: TOPOGRAPHIC CONSTRUALS OF PAST, PRESENT, AND FUTURE IN THE YUPNO VALLEY OF PAPUA NEW GUINEA," BY RAFAEL NÚÑEZ ET AL., IN *COGNITION*, VOL. 124, NO. 1; JULY 2012

The "Time Is Like Space" Metaphor

The puzzle of how humans are able to understand time is an ancient one. Philosopher Saint Augustine put his finger on it in A.D. 400 when he commented: "Who can even form a conception of it to be put in words? Yet what do we mention more often or familiarly in our conversation than time?" Time is slippery and ethereal, but we nonetheless have to grapple with it every day. Only in the past century have researchers started to study human time concepts with an empirical eye, and they started by looking closely at the language people use to talk about time. Benjamin Lee Whorf, famous for his idea that the language you speak guides the way you think, keenly observed in the early 20th century that speakers of English and many other European languages talk of time as "motion on a space" and imagine time units as standing "in a row."

FAST FACTS

HARNESSING THE BRAIN'S SPATIAL REASONING

1. Humans everywhere use spatial metaphors to think about time, but the specifics differ from culture to culture.
2. Even alone in our thoughts, we think of time as space, leaning on brain areas known to play a role in spatial understanding.
3. Culture plays a large role in determining which metaphors we use. The direction of the written word has an especially strong influence.

Whorf also claimed that the Hopi, a Native American tribe, conceived of time in their language without such spatial metaphors. Later researchers showed that spatial metaphors for time are actually rampant in Hopi, just as they are in English. More remarkably, it turns out that *all* human cultures seem to treat time through spatial metaphors (although these metaphors are more or less pronounced across languages). Durations are talked about using words for size ("a short weekend"). Time's passage is treated as movement ("the week flew by"). Events are imagined as located at different positions on a path, in two different ways—by taking an internal perspective or an external one [*see illustration on next page*].

We sometimes imagine ourselves inside the sequence of events, with past, present and future conceptualized as locations where we once were, currently are and will be. This internal perspective on time motivates English expressions such as "the week ahead of us." When we take the external perspective, however, we view the succession of events from the outside, much like watching a lineup of people all moving in one direction. This external perspective motivates phrases such as "a reception follows the ceremony."

These basic ideas about time are expressed spatially in a dazzling variety of unrelated languages, across cultures that differ in every way imaginable. The idea that temporal sequences are like queues of people is found, for example, in Tamil (India), Maori (New Zealand), Greenlandic (Greenland) and Sesotho (South Africa), where the idea that "spring follows winter" can be expressed as "spring is in the footprints left by winter."

But now we come to a wrinkle. Even as people of all cultures lean on spatial concepts for understanding time, exactly *which* spatial metaphors they use can vary. Take the internal perspective, future-in-front metaphor mentioned earlier, found in English and many other languages. This metaphor was long thought to be universal, but in 2006 members of our team investigated a striking counterexample in South America. In Aymara, a language spoken high in the Andes, many phrases suggest the opposite metaphor is at work. For example, the expression "a long time ago" could be loosely rendered in Aymara as "a lot of time in front." Analysis of video-recorded interviews with 30 speakers showed conclusively that Aymara speakers gesture according to this future-behind, past-in-front metaphor [*see box on next page*]. The pattern is especially strong among older speakers who do not speak Spanish, which has the future-in-front metaphor common to English and most European languages.

Elsewhere the divisions between past, present and future are not made according to divisions of the human body at all. In Pormpuraaw, an Aboriginal Australian community, past and future are determined by cardinal directions, with past times to the east and future times to the west. In Yupno, as Danda's gestures made clear, the future is uphill and the past downhill. These different spatial metaphors reflect different cultural preoccupations. Yupno speakers, for example, prefer to carve up the world in terms of uphill and downhill—not completely surprising given the mountainous landscape they call home. They use slopes as points of reference even when this might seem odd to Westerners, such as when inside flat, windowless houses.

Which Way Is Tomorrow?

Spatial metaphors for past and future vary around the world.

LANGUAGE	SPATIAL METAPHOR	BASIS OF METAPHOR
English (and many others)	Past = behind, future = in front	Walking forward
English (and many others)	Past = leftward, future = rightward	Writing, calendars, and timelines
Hebrew	Past = rightward, future = leftward	Writing direction
Mandarin	Past = above, future = below	Writing direction
Aymara (South America), Vietnamese	Past = in front, future = behind	Past is known and seen; future is unknown and unseen
Yupno (Papua New Guinea), Tzeltal (Mexico)	Past = downhill, future = uphill	Unknown
Pormpuraaw (Australia)	Past = east, future = west	Path of the sun

Forward in Time, Forward in the Mind

Although all cultures make use of time-as-space metaphors, a skeptic could counter that spatial metaphors might merely be used for *communicating* about time. Maybe in the privacy of our own minds, metaphors fall away. In fact, peo-

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Where the Future Is Behind

Speakers of Aymara, a language of the Andes, conceive of the past as being in front of them and the future as behind them. The pattern can be seen in everyday language. *Nayra pacha* means "old times," where *nayra* is the word for "eye" or "front," and *pacha* roughly means "time" or "epoch." *Qhipa marana* means "next year," where *qhipa* is the word for "behind," and *mara* is "year." This conception, however, is not just a matter of words. It is also observable in the spontaneous gestures Aymara speakers produce while talking, often pointing backward when referring to future times and forward when discussing the past. What motivates this "reversed" pattern?

For the Aymara, knowledge acquired through visual perception is taken to be certain and reliable. It is of utmost importance to communicate facts and stories by grammatically marking whether what is being said has been seen directly or learned from another source. Aymara people spend much more time talking about past events than about future times. After all, they can tell whether last year was dry or wet—they were there and saw it with their eyes—and can discuss that with clarity and conviction. But how next year is going to be is anybody's guess—nobody has seen it, and so it is just a matter of futile speculation. The known past is therefore conceived as being visually in front of them and the unknown future out of view behind them. ***—K.C. and R.N.***

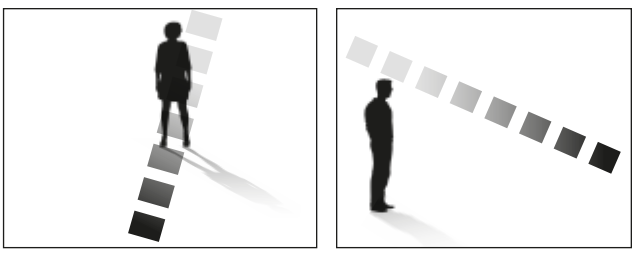
ple draw on space when reasoning about time in all kinds of situations and even when all by themselves.

One line of research has demonstrated this by showing that adults—and even young children—are simply not able to ignore cues from space when asked to judge something about time. For example, when study subjects estimate how long a line was present on a computer screen, the actual length of the depicted line influences how "long" they think the line was visible: longer lines seem to have lingered longer. Other studies have shown that when you ask people to think about time, it can interfere with how they do simple spatial tasks. A 2016 study conducted in Italy asked 19 participants to categorize words such as "yesterday" or "tomorrow" as relating to either the past or the future. Sometimes subjects had to do this categorization by stepping forward when they heard a future word and backward when hearing a past word—consistent with their native metaphor. But other times subjects had to do the opposite, stepping *backward* for future and *forward* for past. In these cases, people were significantly slower to step and made about twice as many errors in categorizing the words. Our team recently obtained similar results with English speakers.

A particularly telling line of research is based on a seemingly simple question: "Next Wednesday's meeting has been moved forward two days. What day will the meeting be on?" Ask a group of people this question, and about half will say Friday and the other half will say Monday. "Forward" is ambiguous when used to refer to time, at least in English. If, using an internal perspective, you imagine next week as something ahead that you are moving toward, then "forward" would mean further into the future, and thus you should respond Friday. But if you externalize time and imagine next week as a lineup of days, with earlier days toward the front of the line, then "forward" would mean earlier in the sequence, and thus you should respond Monday.

Researchers have used this question in more than a dozen experiments, to learn more about how spatial experiences influence thinking about time. In one study, researchers at Stanford University posed the question to more than 300 people at San Francisco International Airport. They found that people who had just gotten off the plane chose more Friday answers when compared with people who were at the airport just to pick someone else up. The experience of moving forward in actual space primed the travelers to imagine "moving forward" in time. In fact, people who were about to get on the plane and were thus merely imagining forward motion also tended to answer Friday. It is also possible to prime people to respond Monday. In one of our studies, people who first answered questions about a lineup of boxes tended to think about time as an external sequence. Forward is earlier in a sequence, so they favored Monday answers.

These findings raise the possibility that parts of the brain used for thinking about space may also be used for thinking about time. Now a handful of studies have provided the first direct evidence for this. In one, published in 2015, researchers in Belgium scanned the brains of participants as they answered questions about the order of events that had recently happened or were about to happen. The researchers found that performing this task engaged a network of brain areas known to support spatial imagery. Another study found that people with



Using spatial metaphors, we imagine time in two ways: as a path we walk with future events in front and past behind (*left*) or as a sequence we view externally, as in summer, fall, winter, spring (*right*).

DADO GALDIERI/*AP Photo (top)*; SOURCE: "THE TANGLE OF SPACE AND TIME IN HUMAN COGNITION," BY RAFAEL NÚÑEZ AND KENSY COOPERRIDER, IN *TRENDS IN COGNITIVE SCIENCES*, VOL. 17, NO. 5; MAY 2013 *(bottom)*; © ISTOCK.COM (*woman* and *man icons*)

WRITTEN LANGUAGE HAS A BIG IMPACT. HEBREW READERS SEE TIME MOVING FROM RIGHT TO LEFT; CHINESE IMAGINE TODAY ABOVE TOMORROW.

damage to space-related brain areas also have trouble thinking about time. When we take an external perspective on time, in English and many European languages, we often imagine past events to the left and future events to the right. Accordingly, the study found that people with disrupted spatial abilities on their left side had trouble remembering past events and even confused past events for future ones.

The Influence of Writing

The time-as-space metaphor shows up in our language and gestures, and it is active in our minds even when we are not communicating about time. It also shows up with striking clarity in depictions of external sequences of events, which have come to saturate every aspect of our visual culture. Histories are laid out on timelines. T-shirts riff on the iconic image of human evolution as proceeding rightward, creature by creature. No matter whether your calendar is printed or digital, it no doubt shows the days arranged from left to right and the weeks from top to bottom.

The most subtle representation of time unfolding is written text, and it may also be the most powerful. Regardless of what script you are using, the symbols are presented in linear order. For instance, Latin script, as used in English, proceeds from left to right—thus earlier symbols are to the left of later symbols—and this guides intuitions about which way time flows. If you have people arrange three temporally ordered images—a banana in its peel, the banana partially peeled and the banana half-eaten—English speakers will lay them out from left to right, but Hebrew speakers will lay them out from right to left, echoing how Hebrew is written. Mandarin Chinese speakers refer to "last week" as above and "next week" as below, which stems from the fact that Mandarin is traditionally written vertically, from top to bottom. Moreover, blind people develop a left-to-right model of time based solely on their experience reading Braille, which flows from left to right.

Writing is so powerful, in fact, that one study found that it is possible to reverse time's imagined "direction" by training people to read writing that had been mirror-reversed. The researchers had Dutch participants categorize words as being related to the past or the future, much like the stepping study described earlier but with button presses instead of steps. In general, people were faster to categorize past events by pressing a button on the left and future movements by pressing a button on the right. But after just a few minutes of reading mirrored text, they showed the opposite pattern. Graphical practices, where they are used, can thus shape our conceptions of time in powerful ways. Reading and writing, however, are not needed to develop the intuition that time can be thought of spatially, as evidenced by Aymara, Yupno and other cultures that lack writing traditions but that nonetheless spatialize time. Such cultures offer clues about how time has been grasped since before the invention of writing.

The Future of Time

Time may be the abstract concept we use the most—in the words of one scholar, J. T. Fraser, it is a "familiar stranger." This makes time a critical case study for understanding the human capacity for abstract thinking, a hallmark of our species. But time is not the only abstract domain, nor is it the only one we understand through metaphor. For some ethereal notions, we use metaphors based on color, weight, heat or even sound—such as when we feel heavy-hearted or boiling mad. But spatial metaphors are particularly common, structuring how we think about not only time but also causation and kinship, politics and power (as in the phrase, "she has the upper hand"). Why is space at the root of so many metaphors? Space is something humans have evolved to be especially good at navigating, and our brain has an elaborate system for mapping it. When we think about, talk about and depict abstract ideas as spatial in nature, we are capitalizing on hard-won cognitive talents.

The human reliance on spatial metaphors for abstract thinking may have deep evolutionary roots and is not likely to change any time soon. The particular metaphors we lean on, however, are a product of culture—not of biological evolution—and are much more malleable. Literacy is a recent and rapid achievement in the scope of the human saga, but it already has had profound consequences for how people conceptualize time. New spatial metaphors for our dearest abstract concepts will almost certainly enter the picture as our culture evolves. E-mail in-boxes show the most recent items at the top, but text messages go the other way, with the newest at the bottom. And so we must wonder: Which way will time flow next? M

MORE TO EXPLORE

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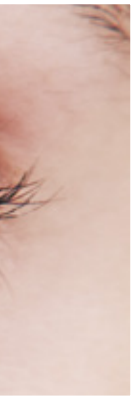

In Search of Hidden Minds

Finding signs of consciousness among severely brain-injured patients is medically challenging—and morally imperative

By Joseph J. Fins and Nicholas D. Schiff

We both stood anxiously at Maggie Worthen's bedside, trying to determine if this 23-year-old patient might be able to communicate with us. Nearly two years had passed since the cataclysmic stroke that left her almost entirely paralyzed. We asked her if the woman at the foot of her bed was her mom and instructed her to look down if the answer was yes. We waited, watching Maggie carefully. After several seconds, she replied, gazing slowly downward with her left eye. The movement was subtle but deliberate—a clear response, full of meaning and emotion.

A stroke left Maggie Worthen in a minimally conscious state, but she regained a limited ability to communicate and even paint—with hand-over-hand help from her mother, Nancy.

It was a stunning breakthrough. Most of the doctors who treated Maggie after her stroke thought she was in the vegetative state, a condition in which people's eyes are open, but they have no awareness of themselves, others or their surroundings. Such patients are normally viewed as lost to their families and unable to recover. One doctor, though, had diagnosed Maggie as being in the minimally conscious state (MCS), in which people show inconsistent signs of awareness, such as responding to their name one day but not the next. This observant doctor had noticed that sometimes—but only sometimes—Maggie tracked moving objects with her left eye.

So Maggie and her mother, Nancy, traveled to see us at Weill Cornell Medicine in New York City, where we have been investigating how the brain recovers from what are known as disorders of consciousness. This label encompasses a range of states, including coma, the vegetative state, MCS and so-called locked-in syndrome [*see box on next page*].

Nancy agreed to let Maggie participate in our research and also to let us tell their story here. Over the course of Maggie's evaluation, Nancy learned that her daughter was indeed conscious and that she knew who Nancy was. Armed with that information, Nancy was able to get Maggie greater rehabilitative care. Mother and daughter pursued speech and art therapy. And before Maggie's death in August 2015 from complications related to pneumonia, she was regaining some ability to interact and had even spoken a few words—something that would have never been possible had Nancy accepted the initial verdict that her daughter was in the vegetative state.

Maggie's case frames many of the ethical and scientific challenges we in the medical community and society at large face when it comes to patients who

FAST FACTS

MAKING CONTACT

1. Patients with disorders of consciousness, including those in the so-called minimally conscious state, are often presumed to be in a permanent vegetative state—an error that limits their access to rehabilitation and any chance at recovery.
2. These patients can be difficult to identify because their awareness of themselves, others and their surroundings breaks through only episodically and inconsistently.
3. Interventions that stimulate the brain networks involved in consciousness, though, are helping some severely brain-injured people regain the ability to communicate.

PAGE 44: STEPHEN SMITH *Getty Images (composite)*; THIS PAGE: COURTESY OF NANCY WORTHEN

appear unconscious or barely responsive but might still harbor high-level cognitive function. Historically, these individuals have been relegated to nothing more than "custodial care," but we now have better options: improved imaging technology, interventions using deep-brain stimulation and certain medications are providing new ways to identify and reach out to conscious patients among the severely brain-injured. As our capabilities increase, so does our obligation to help these people reestablish relationships severed by injury.

Too Little, Too Soon

Maggie sustained her injury in 2006, just a week before her graduation from Smith College. Fighting for her life in a nearby hospital, she received her degree in Spanish in absentia while her classmates marched, all wearing little blue ribbons in her honor. Against the odds, Maggie survived those first few weeks, and her mother ignored repeated pleas to withhold or withdraw care. Maggie moved from acute care to rehabilitation to a nursing home, and there she lingered—among patients who were mostly decades older—until she came to New York.

Sadly, Maggie's journey is typical. After receiving brilliant, lifesaving emergency care, people with disorders of consciousness are routinely tracked into less aggressive treatment before their prognosis is clear. In *Rights Come to Mind: Brain Injury, Ethics, and the Struggle for Consciousness* (Cambridge University Press, 2015), one of us (Fins) chronicled Maggie's story and how our health care system tends to marginalize patients with severe brain injury, presuming that nothing can or perhaps should be done. More than 50 families interviewed for the book shared how brain-injured relatives were often subjected to premature palliative care recommendations. If they did manage to qualify for rehabilitation, it was too little, too soon; many were not completely stable when they were discharged from the hospital and struggled with ongoing medical issues.

Eventually many people with disorders of consciousness wind up, as Maggie did, in a nursing home, which can put their lives at risk. Chronic care settings are often poorly equipped to provide the kind of sophisticated medical surveillance these patients need. And because they receive no further rehabilitation, nursing home care limits their potential recovery. Spontaneous improvement from the vegetative state becomes rare after three months to a year, depending on the type of initial injury. Before that, though, some patients do begin to recover from the vegetative state, shifting into a minimally conscious state.

Unfortunately, that transition can go unnoticed. One notable study in 2009, by Caroline Schnakers of the University of Liège in Belgium and her colleagues, found that 41 percent of 44 patients thought to be in a vegetative state were in

Disorders of Consciousness

Coma
Many serious conditions—from poisoning to heart attack to brain injury—can lead to coma, which may have evolved as a way to protect neurons from death. Comatose patients do not open their eyes or respond to stimuli—even painful ones. Nor do they have a sleep-wake cycle. They show no cognitive or motor function.

Vegetative State
Coma patients can progress to a vegetative state, in which they intermittently open their eyes but still have no cognitive or motor function. Although many patients do emerge from the vegetative state, it is considered more likely to be permanent after anywhere from three months to a year, depending on the underlying cause.

Minimally Conscious State
Patients who surface to the minimally conscious state begin to show fleeting signs of awareness. They can sometimes follow commands, make gestures or show other nonreflexive behaviors. For instance, they may smile or laugh at an appropriate time or respond to their name.

Cognitive Motor Dissociation
This proposed category would apply to a subset of patients who appear to be in a coma or a vegetative or minimally conscious state but display clear cognitive activity when examined via brain imaging or similar technologies. Without a two-way communication channel allowing such patients to respond and initiate dialogue, it is impossible to gauge their level of consciousness.

Confusional State
As people recover consciousness, they may pass through a confusional state, in which they appear disoriented. These patients have a limited range of cognitive function but cannot yet be formally tested using standard neuropsychometric measures.

Locked-in Syndrome
In this condition, people have normal conscious awareness but severe motor impairment, limiting their ability to communicate. As made famous by the memoir and film *The Diving Bell and the Butterfly,* some locked-in syndrome patients can use coded eye movements to communicate, but new brain-interface technologies may offer them improved options. These patients rarely recover any motor control.

New techniques make it easier to find conscious patients among the severely brain-injured—upping our obligation to help them.

fact minimally conscious. This alarming error rate can be attributed to several factors. Diagnostic criteria for MCS have existed only since 2002, and it is difficult for busy care staff to observe consciousness that breaks through only episodically. Part of it may also stem from the right-to-die movement in the U.S. In 1976 Chief Justice Richard Hughes of the New Jersey Supreme Court justified the removal of Karen Ann Quinlan's ventilator because she had "no realistic possibility of returning to any semblance of cognitive or sapient life."

That view holds true only for people who, like Quinlan, are permanently in the vegetative state. But it is often extended to many more patients with different disorders of consciousness, who can improve—sometimes dramatically, even decades after their original brain damage.

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Perhaps the most famous example is Terry Wallis, who was minimally conscious for 19 years after a car accident before recovering speech and near-normal cognition. We made substantial efforts over the course of several years to establish reliable communication with Maggie, and she made significant, if inconsistent, progress. A detailed look at her injuries—and the unique challenges they posed to her recovery—shows why the routine neglect of minimally conscious patients is both scientifically confounding and ethically problematic.

Regaining Awareness

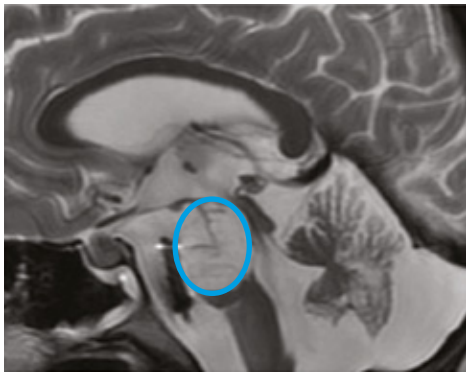
Maggie was an otherwise healthy college senior when she suffered a rare event of unknown origin. A large clot blocked off the single artery supplying blood to most of her brain stem, causing widespread damage there. Because nearly all the descending motor fibers to her spinal cord passed through this damaged area, she was left with almost no ability to move any part of her body. Maggie's massive brain stem injury also harmed nearby structures that normally send arousal inputs from the brain stem to the corticothalamic system, supporting overall levels of activity during wakefulness.

In addition, Maggie had two small but crucially placed injuries in the central regions of both thalami, egg-shaped masses at the base of the brain that serve as a kind of information hub. The central thalamic neurons in particular have extensive connections to the frontal cortex, which carries out many tasks, including planning. In any multifocal brain injury, the central thalamic neurons receive less input and, as a result, become structurally and functionally impaired, but in Maggie's case, they were directly compromised, too. In essence, she presented with a more serious version of a core problem within the central thalami that many severely brain-injured patients face.

These neurons form the key node in what is called the anterior forebrain mesocircuit—linking the thalami, frontal cortex and basal ganglia [*see illustration on next page*]. The network as a whole helps to regulate levels of arousal and, during wakeful periods, allocate attention. In this way, it supports a wide range of cognitive functions. Research suggests that getting the anterior forebrain mesocircuit back online is crucial for regaining consciousness, and the level of its function tracks with a patient's level of behavioral recovery. But reactivating the central thalamic neurons after severe brain injury is challenging for two reasons: not only are they physically less connected and receiving less stimulation than usual, but abnormal overactivity of parts of the basal ganglia also inhibits their output.

Also, the anterior forebrain mesocircuit is not the only network in play. Neurologist Steven Laureys of the University of Liège and his colleagues have found an even stronger graded correlation between recovering consciousness and metabolic activity in the posterior medial parietal complex (PMC), the main component in the brain's frontoparietal network. This region exhibits the highest resting metabolic rate in the human brain. Neurologist Marcus Raichle of Washington University in St. Louis and his colleagues have hypothesized that it supports a default-mode network, responsible for maintaining and updating consciousness with relevant contextual information, and helps us to interpret sensations and predict actions. The default-mode network is also associated with self-monitoring and access to personal memories.

Maggie had no specific damage to the PMC, but we have found evidence that it works in tandem with the anterior forebrain mesocircuit to support the recovery of consciousness. Other researchers have found that altered structural connections between the thalami and the PMC are statistically linked to behavioral outcomes: the more wiring between the two, the greater a patient's awareness. Scientists have also found a functional



Two scans reveal the extent of Maggie's stroke. A large clot blocked the single artery supplying blood to her brain stem, causing widespread damage (*circled, top left*). Because nearly all the nerve fibers from her motor cortex to her muscles passed through this area, she was almost completely paralyzed (*bottom left*). She also suffered two injuries to the central thalami (*circled, top right*), a key component in the anterior forebrain mesocircuit (*bottom right*). This network, along with the posterior medial parietal complex (PMC), is critical to maintaining consciousness. Maggie's injury, plus abnormally strong inhibitory signals from the basal ganglia, muted communication within this network.

COURTESY OF NICHOLAS D. SCHIFF (*brain scans*); ©ISTOCK.COM (*motor system*); SOURCE: "DISORDERS OF CONSCIOUSNESS AFTER ACQUIRED BRAIN INJURY: THE STATE OF THE SCIENCE," BY JOSEPH T. GIACINO ET AL., IN *NATURE REVIEWS NEUROLOGY*, VOL. 10; FEBRUARY 2014 (*anterior forebrain mesocircuit diagram*)

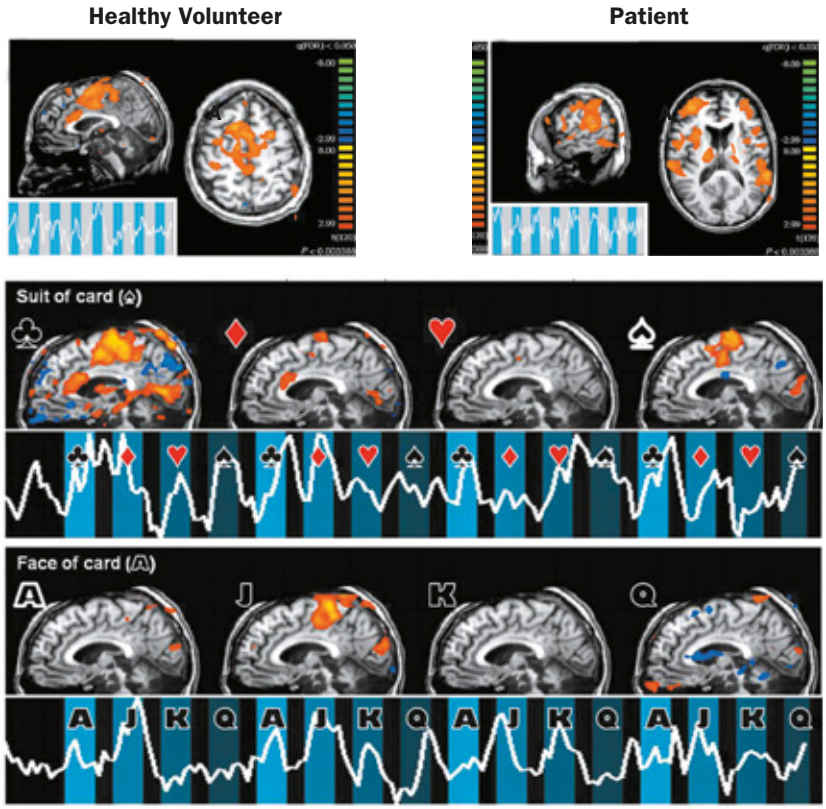
tie. In experimental studies, researchers at McGill University anesthetized healthy volunteers and then gave them drugs to induce a moment of consciousness. The subjects could respond to commands even though the level of anesthesia was held constant, and this brief awakening was linked to greater activation in both the central thalami and the PMC.

Reading Minds

Maggie's injury to the central thalami, in combination with her extensive brain stem injury, created a very challenging path to making or recognizing recovery. Recently, though, we have made significant advances in our ability to assess patients with severe brain injuries. Now we can ask them to carry out specific mental actions and view their response, if any, via functional MRI, electroencephalography (EEG) and related techniques. Even among patients who show limited or no overt signs of consciousness, these methods can offer proof of volition and awareness.

The first such example came in 2006. Neuroscientist Adrian M. Owen, now at the University of Western Ontario, and his colleagues at the University of Cambridge and the University of Liège worked with a 23-year-old woman who was considered vegetative after a car accident. Based on behavioral criteria, she showed no awareness or response to commands. But when they placed her in an fMRI scanner and asked her repeatedly to imagine playing tennis, the resulting images showed strong, consistent patterns of brain activation within the supplementary motor area of the frontal lobe. They noted that the same locations lit up in healthy volunteers who were asked to imagine the same activity.

Our group has used versions of this approach in a few brain-injured people—including Maggie. To evaluate her capacity to register information and respond, we initially asked her to imagine different motor tasks. Her results showed that she produced very strong patterns of brain activation when we asked her to imagine swimming, which had been one of her favorite sports. These patterns were comparable to those of normal subjects. We also found that Maggie could activate the same regions to answer ques-



A Card Trick to Detect Cognition

When we examined Maggie using functional MRI, we found clear evidence of her hidden cognitive abilities. First, we asked her to imagine swimming, which had been one of her favorite sports. Her brain showed increased blood flow primarily in the supplementary motor area (*top row, right*). A healthy volunteer who also imagined swimming generated a similar pattern of brain activation (*top row, left*).

Next we tested whether Maggie could use this same mental activity to answer a multiple-choice question about playing cards. We asked her to imagine swimming when the suit or face we showed her matched the ace of spades. Initially she seemed to answer affirmatively to both the club and spade, but an analysis revealed that only her response to the club was statistically significant. So, too, she appeared to respond to the jack, not the ace. But we later found evidence suggesting that she had answered correctly and that her injuries had caused a one-card delay.

tions, such as picking the suit or face of a playing card from four choices.

At first, though, her responses were confounding. A statistical analysis showed that her answers were not just the product of chance, but they did not appear to be accurate either [*see box above*]. We speculated that perhaps her replies were somehow delayed. So we reanalyzed the data and discovered evidence that her intended responses had been coming in one question late. When we shifted Maggie's responses back a question, they were correct. We knew that isolated central thalamic injuries such as hers could slow down cognitive processing, but the finding still came as a surprise—and served to underscore once more the complexity of assessing patients like Maggie.

Hope for Recovery

Outcomes following severe brain injuries fall on a continuum, but researchers have identified two types of patients who are more likely to regain at least some level of communication. One subset includes minimally conscious patients with a certain base amount of reserve in their remaining corticothalamic systems, as assessed by brain imaging. In 2007, in collaboration with colleagues at various institutions, we helped one such patient who had been minimally conscious for six years.

Over the course of six months we used deep-brain stimulation (DBS) to repeatedly apply a small electric current directly to his central thalami. After the treatment, this individual regained spoken language, the ability to direct his attention, motor control, and the ability to chew and swallow. The DBS regimen had activated the central thalamic neurons enough to rouse the patient from MCS into a behavioral range best described as a confusional state. With continued stimulation—the device was left on during the day—his gains were sustained for six years until he died from pneumonia.

Researchers have also studied medications such as amantadine, an antiviral drug also used to treat Parkinson's disease, and the sedative zolpidem, among others. These pharmacological interventions have helped several other MCS patients regain communication, either intermittently or as part of a more enduring recovery. Similar to the DBS approach, the compounds are known to activate neurons across the anterior forebrain mesocircuit.

In contrast, Maggie exemplifies a second class of patients—with very severe injuries to the motor output systems of the brain but less severe injury within the corticothalamic system—

FROM "DISSOCIATIONS BETWEEN BEHAVIOURAL AND FUNCTIONAL MAGNETIC RESONANCE IMAGING–BASED EVALUATIONS OF COGNITIVE FUNCTION AFTER BRAIN INJURY," BY JONATHAN C. BARDIN ET AL., IN *BRAIN*, VOL. 134, NO. 3; MARCH 1, 2011

We now segregate disabled conscious people in our health care system, denying them the chance to rejoin their communities.

who may stand an even better chance of regaining reliable communication because they retain more covert cognitive function. One of us (Schiff) has proposed the term "cognitive motor dissociation" (CMD) to describe them. These patients fulfill the behavioral criteria for coma, vegetative state or minimally conscious state, but when they are evaluated using fMRI or EEG, they show that they can follow commands by imagining actions and producing specific patterns of brain activity.

More important, the tests cannot fully reveal cognitive capacity. These patients cannot initiate communication, ask questions or engage in a dialogue in the same way that locked-in syndrome patients can. But recent studies looking at EEG activity during sleep and wake states, as well as cerebral metabolic activity, strongly support the idea that brain function in CMD patients more closely resembles that of healthy control subjects and locked-in patients than minimally conscious patients who can only communicate or follow motor commands intermittently.

CMD patients such as Maggie whose cognitive capacity is dissociated from their motor function present the most profound ethical challenge. Damage to the anterior forebrain mesocircuit, particularly injuries to the central thalami, leads to a fluctuating ability to stay alert and sustain attention, which can put dormant cognitive resources out of reach. It is difficult to assess what these patients are aware of and to figure out how to reestablish two-way communication.

The Right to Reintegration

Patients like Maggie need more than physiological reintegration to recover. They need societal reintegration as well. Currently we segregate disabled conscious individuals in the health care system, treat them as if they are not aware and deny them the opportunity to participate in civil society. But that opportunity is a basic human right they hold under our prevailing laws. Both the Americans with Disabilities Act and the United Nations Convention on the Rights of Persons with Disabilities assert that individuals with disability have the right to be maximally integrated.

Segregation is a strong word, and we use it advisedly. For physical disabilities, it can mean the inability to access public accommodations for want of a ramp. For disorders of consciousness, it is the denial of a voice, which is nothing short of a proxy for consciousness. Patients with disorders of consciousness cannot be reintegrated into their communities unless we restore to them some form of functional communication. Note the cognates—communication and community. One enables the other and helps patients with disorders of consciousness return to the nexus of their homes and families.

Physicist and novelist C. P. Snow once said that "scientists have the future in their bones." We must be forward-looking when considering therapeutic interventions for CMD patients. Their variable levels of arousal and attention mean that it may be difficult for them to use standard augmentative communication technologies. But before her death, Maggie was well on her way to using a system with a high-resolution, fast closed-circuit camera, which improved her learning using rapid auditory feedback and enabled some communication, with her generating downward eye movements. It was real progress from where she had been but just a small step toward reliable engagement with the outside world.

We anticipate that faster and more reliable feedback technologies, now in use with locked-in patients, will be able to help some CMD patients communicate reliably. Once even one of these patients crosses that threshold, it will be hugely significant—even historic. In that moment, isolation, segregation and silence will no longer be their plight; rights will then come to mind for patients who have for too long had them abridged. **M**

MORE TO EXPLORE

- **Disorders of Consciousness after Acquired Brain Injury: The State of the Science.** Joseph T. Giacino et al. in *Nature Reviews Neurology,* Vol. 10, No. 2, pages 99–114; February 2014.
- **Preservation of Electroencephalographic Organization in Patients with Impaired Consciousness and Imaging-Based Evidence of Command-Following.** Peter B. Forgacs et al. in *Annals of Neurology,* Vol. 76, No. 6, pages 869–879; December 2014.
- **Cognitive Motor Dissociation Following Severe Brain Injuries.** Nicholas D. Schiff in *JAMA Neurology,* Vol. 72, No. 12, pages 1413–1415; December 2015.
- **Frequency-Selective Control of Cortical and Subcortical Networks by Central Thalamus.** Jia Liu et al. in eLife, Vol. 4, Article No. e09215; December 10, 2015.
- **Rights Come to Mind: Brain Injury, Ethics, and the Struggle for Consciousness.** Joseph J. Fins. Cambridge University Press, 2015.

From Our Archives

- **Is Anybody in There?** Adrian M. Owen; *Scientific American,* May 2014.

The Art of Neuroscience

Stunning images from an annual competition reveal the beauty of a complex science

By Sara Chodosh

Photo Editing: Liz Tormes

Ink, watercolors and pencils may not seem like critical tools for neuroscientists. Yet these were the implements that helped Santiago Ramón y Cajal, the father of modern neuroscience, discover that neurons are the main functional unit of the brain. His intricate drawings of brain cells served as a lens through which he could examine how their structure dictated their function.

Ramón y Cajal's late 19th- and early 20th-century sketches were nothing like the bland illustrations that fill most modern textbooks. They were works of art in their own right—with delicate snaking tendrils of black ink branching out from individual cell bodies and becoming tangled with neighboring neurons. They are still heralded for their power to showcase the inherent beauty of the nervous system.

Today's illustrative tools are more technical. Scientists use chemical stains to imbue cells with a fluorescent glow or imaging machines to highlight brain activity with bursts of color. But the results are often the same: spectacular visuals that help us better understand the inner workings of our mind.

Few images gathered in the course of research ever escape the lab, but the annual Art of Neuroscience Competition helps to bring some to light. The contest, organized by Tycho Hoogland, Chris Klink and Cathrin Canto, all at the Netherlands Institute for Neuroscience, recognizes one grand prize winner and four honorable mentions from a wide selection of submissions, all intended to join art with science in some way. What follows is a subset of this year's entries—some winners and others we felt were particularly beautiful or revealing. All the submissions are available to view at http://aon.nin.knaw.nl.

THE AUTHOR

SARA CHODOSH is a science journalist and editorial intern for *Scientific American Mind* who writes frequently about neuroscience. Her work has also been featured in *Undark* and the *Atlantic*.

Grand Prize Winner

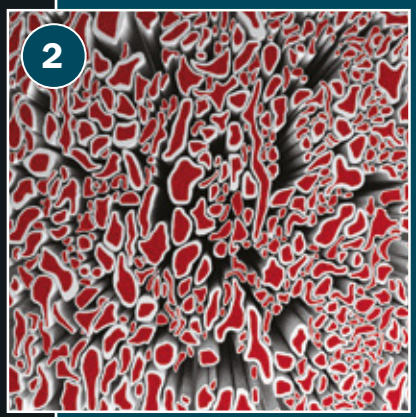
1. THE MUTUAL WAVE MACHINE

You are enveloped in darkness. A spray of light erupts in front of you, cast onto a translucent white screen. It pulses as it coalesces into a face—your face. This spectacle is the Mutual Wave Machine's grand finale, seen only by partners who, when sitting inside the contraption together, can get literally on the same wavelength. Headsets measure each person's brain waves using tiny EEG monitors. As their frequencies align, patterns emerge in the projected light. Greater synchrony produces more vivid images, progressively morphing into images of their faces.

Researcher Suzanne Dikker of New York University and Utrecht University in the Netherlands and artist Matthias Oostrik created the installation, which has now been exhibited around the world. It makes immediate what is usually amorphous: a personal connection between two people.

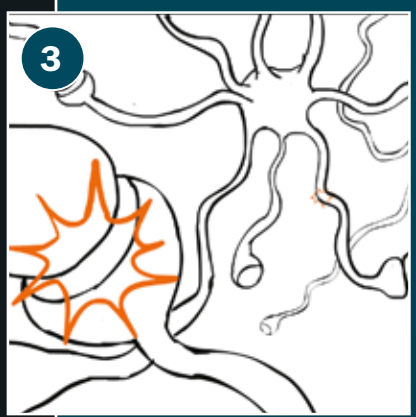
This face was generated by the Mutual Wave Machine. Ghostly and patterned, it looms out of the darkness, vaguely surreal and yet immediately recognizable.

Honorable Mentions



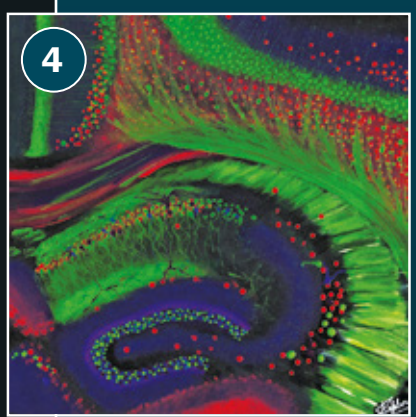
2. AXONS IN SHAPE

A protein called myelin insulates axons to make them better electrical conductors. In this cross section, prepared by postdoctoral MRI physicist Michiel Kleinnijenhuis of the University of Oxford, a cluster of individual axons appears red, with sheathes of white myelin wrapped around them. The view makes it easier to see their variable size and shape. The diameter and density of an axon, among other properties, determine how well it works and are useful measures in studying brain functionality.



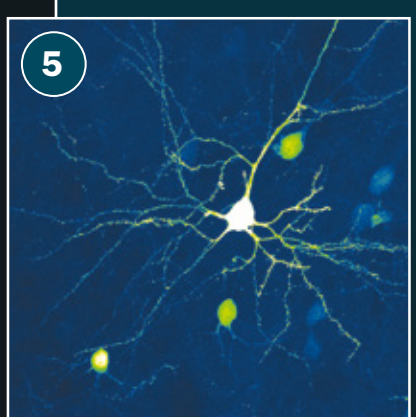
3. EXPLODING BRAIN MYTHS

Brains are enormously complex, and myths about them abound: We only use 10 percent of our brain. Left-brained people are more logical, right-brained more artistic. There is one hormone that makes us fall in love. And so on. Neuroscientist Rhiannon Meredith of VU University Amsterdam in the Netherlands created a video series, available via YouTube, to set the record straight. This still image comes from the final video, which explains why brain-training games do not increase your overall intelligence. Learning something new is thought to change only those cells directly involved in the activity, as shown in the illustration.



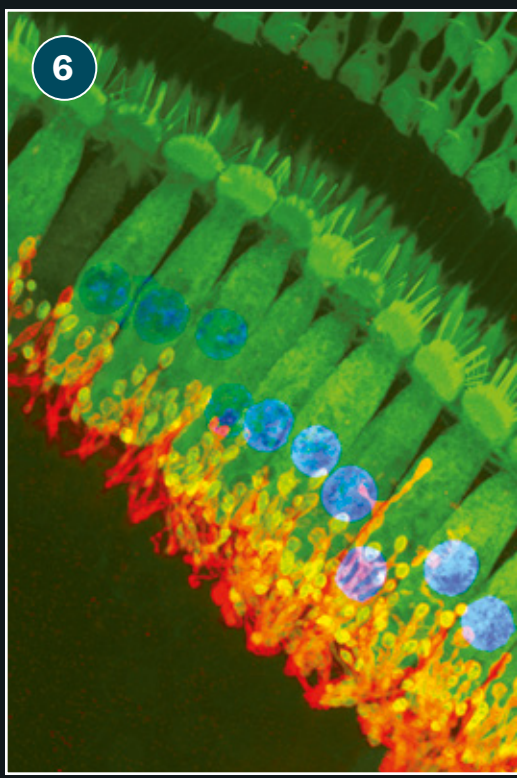
4. AURORE BOREALE

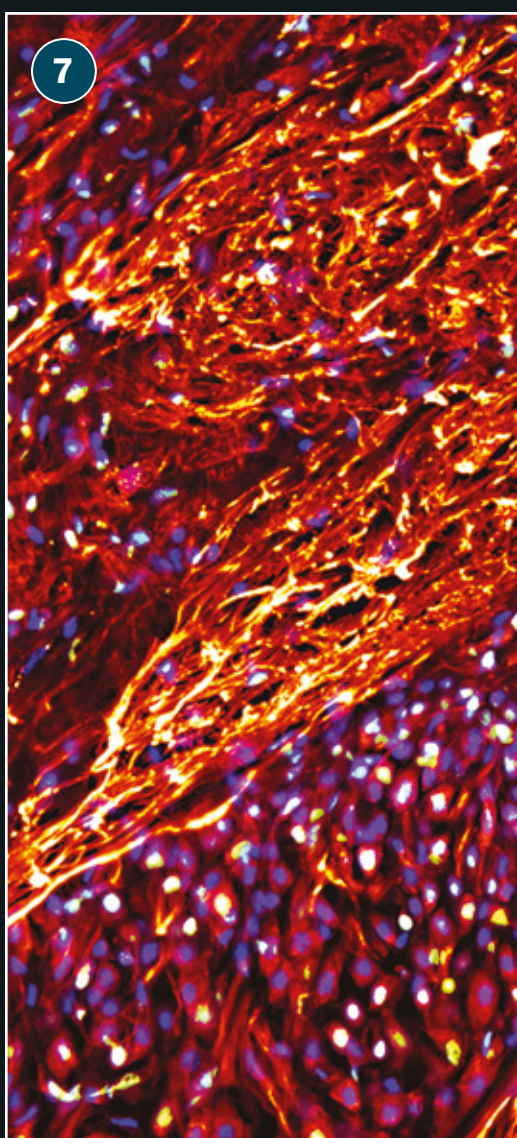
In this painting by French artist Alicia Lefebvre, a slice of the hippocampus resembles the famous Northern Lights. This brain region has well-defined layers, each of which features particular types of cells, depicted here in different hues. These cells serve relatively distinct roles in memory consolidation—the process by which the brain converts memories from short to long term. The area is also one of the first to be damaged in Alzheimer's disease.

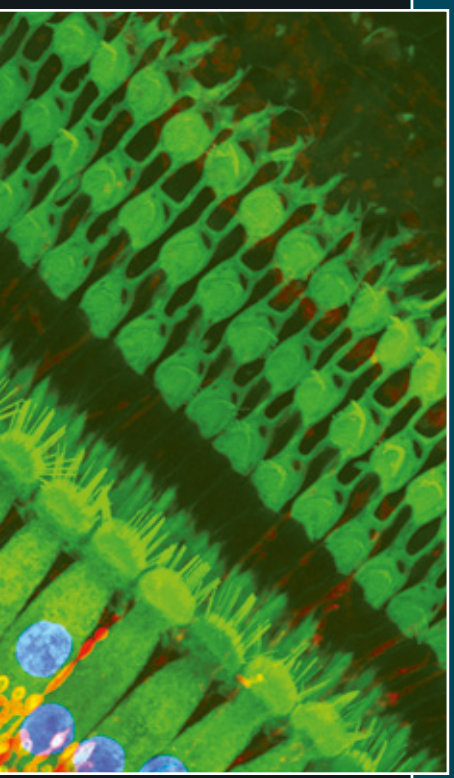


5. BUTTERFLY OF THE SOUL

Santiago Ramón y Cajal described neurons as "mysterious butterflies of the soul," a phrase that research assistant Robin Scharrenberg says stuck in his mind as he studied mouse pyramidal cells, such as the one shown here, under the microscope at the Center for Molecular Neurobiology Hamburg at the University Medical Center Hamburg-Eppendorf in Germany. He was trying to understand how structural changes in these cells—one of the most common neurons in the neocortex—might contribute to functional changes akin to those found in autism spectrum disorder. As is clear from this image, pyramidal cells typically feature a long axon that stretches out to deliver signals to other cells and shorter, branched dendrites that stay close to the cell body to receive messages.







Editors' Picks

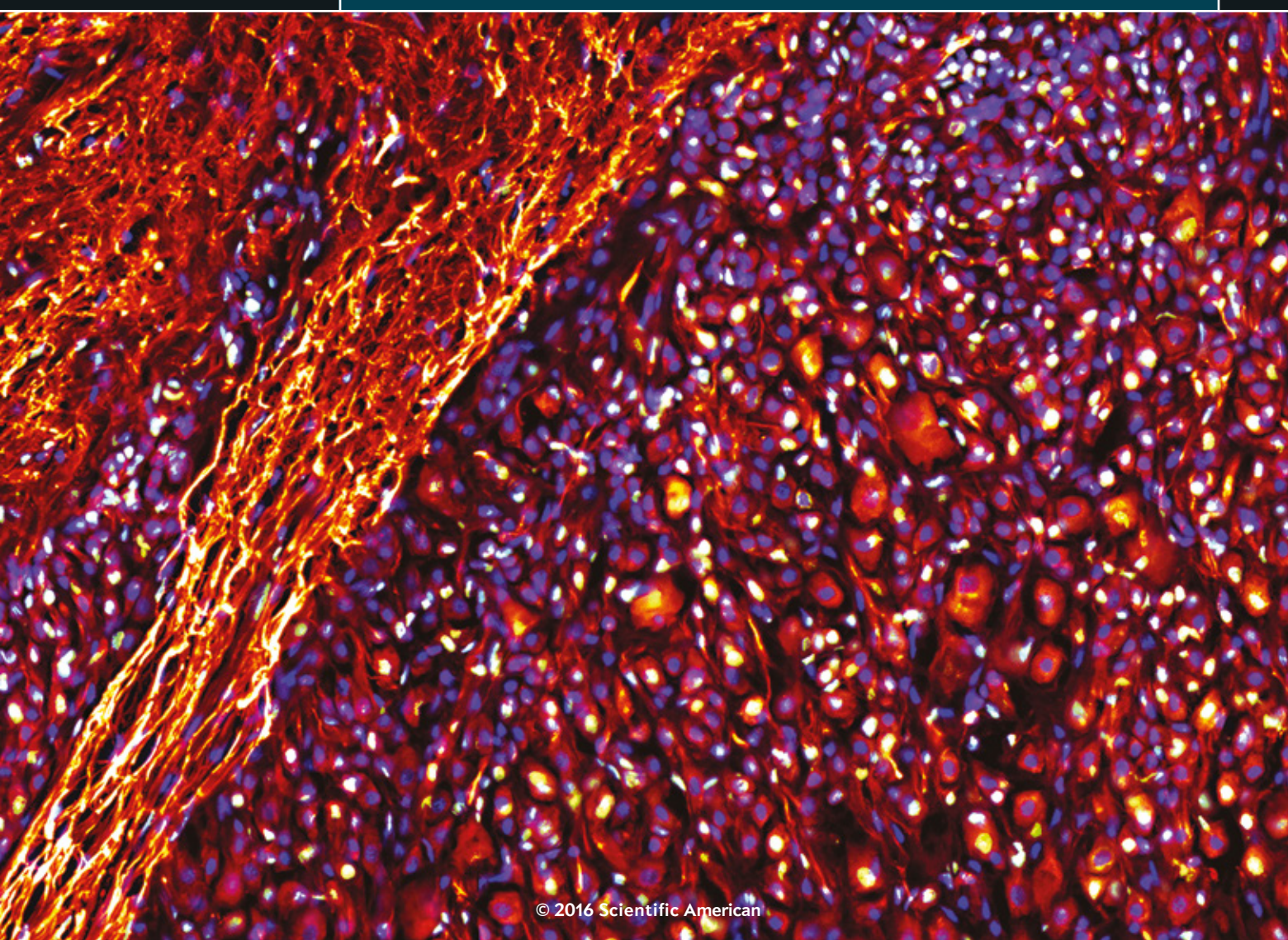
Perhaps the best works of art are those that reveal some truth about their content. *Scientific American Mind* editors selected the following images not only for their visual appeal but also for what they reveal about the brain. They represent a range of scientific ideas and imaging techniques and sit at the very intersection of art and neuroscience.

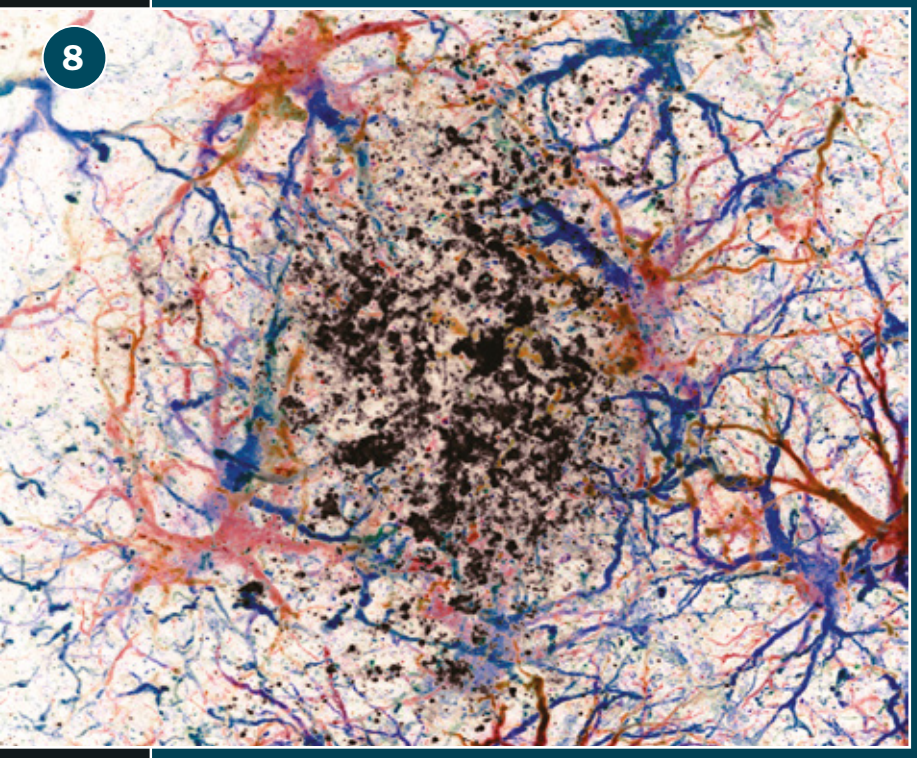
6. SYNAPTIC SENSE OF SOUND

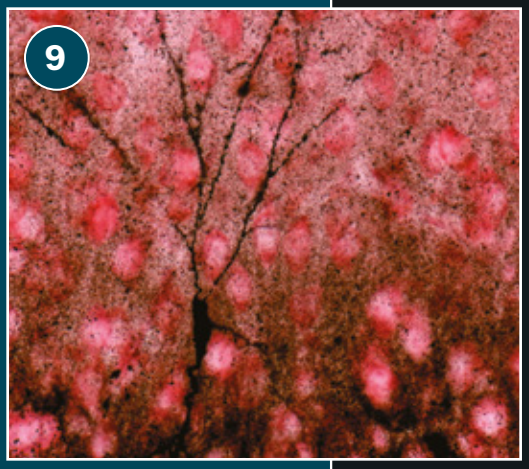
When we hear a sound, it enters the ear as a physical wave in the air but must become a chemical signal for our brain to understand it. Hair cells—shown here in green—perform that critical translation. These cells have tiny, fingerlike protrusions that wiggle as waves pass them by. This movement opens and closes minuscule channels in the cell, starting an electrical signal—which in turn becomes a chemical neurotransmitter signal—that travels to the brain's auditory-processing areas for interpretation. Neuroscientist Sonja Pyott of the University Medical Center Groningen in the Netherlands used fluorescent markers to highlight each structure as part of her research on preventing and reversing hearing loss.

7. STELLATE GANGLION ON FIRE

Between the brain of an octopus and its peripheral nervous system sits a collection of nerves called the stellate ganglion, shown here in reddish-orange. Only two pallial nerves connect to the stellate ganglion. Severing one eliminates muscle control, but thanks to advanced regeneration abilities, the octopus can regrow nerves and regain the connection in just a few months. This image, created by Ph.D. student Pamela Imperadore of the Stazione Zoologica Anton Dohrn in Naples, Italy, shows a stellate ganglion only a few days after one nerve was severed.







8. MOMENTS MEANT TO PASS

The smattering of black in this image looks like a harmless splash of paint but is actually one of the key agents behind Alzheimer's. Amyloid plaques—clumps of misfolded proteins that form in the spaces between neurons—can develop in normal brains. If they are not cleared and start to accumulate, though, they disrupt brain function. This image by Luke Maninov Hammond, microscopy facility manager at Queensland Brain Institute in Australia, came from a study conducted by Jürgen Götz and his colleagues investigating whether ultrasound could reduce amyloid plaques in mouse brains. Red and blue microglia cells, the primary type of immune cell in the brain, stand in contrast with the black plaque.

9. BRAIN IMPRESSIONISM

This black, scraggly neuron, floating in a sea of pink, resembles a dying tree—and in fact, it is degenerating. Its color comes from a stain called amino-cupric silver, which was originally used to identify neurodegenerative disorders because only dying neurons absorb it. Neuroscientist Soledad de Olmos of the Medical Research Institute Mercedes and Martin Ferreyra in Argentina made the image by infecting a mouse with a virus that causes brain inflammation, which can make neurons too excitable. This overexcitability can cause excitotoxicity, in which nerve cells fire so frequently as to damage their own structure. Excitotoxicity is involved in a number of neurodegenerative disorders such as Alzheimer's, multiple sclerosis and amyotrophic lateral sclerosis.

10. HEART SPACE

In this image, artist Elizabeth Jameson reclaims the brain scans used to diagnose and track her own case of multiple sclerosis. This particular scan is a type of MRI called diffusion tensor imaging that looks at the flow of matter in the brain. As Jameson played around with the scan, she stumbled on this image of a heart, which filled her with an instantaneous sense of wonder. She says she was uplifted by this symbol of love and compassion embedded in an analytic scan of her diseased brain.

OLEG BORODIN (*1*); COURTESY OF MATTHIAS OOSTRIK (*inset in 1*); MICHIEL KLEINNIJENHUIS *FMRIB, University of Oxford* (*2*); COLLABORATION BY RHIANNON MEREDITH, RHODÉ VAN WESTEN AND MATTHIJS VERHAGE AND ANIMATORS JON HUNTER, MATT PARTRIDGE, HENRY PAKER AND GARETH GWYNN; FUNDED BY A VU UNIVERSITY RESEARCH FELLOWSHIP AND A NETHERLANDS ORGANIZATION FOR SCIENTIFIC RESEARCH AWARD (*3*); COURTESY OF ALICIA LEFEBVRE (*4*); ROBIN SCHARRENBERG *RG Neuronal Development, Center for Molecular Neurobiology Hamburg (ZMNH), University Medical Center Hamburg-Eppendorf* (*5*); SONJA PYOTT *Department of Otorhinolaryngology, University Medical Center Groningen* (*6*); PAMELA IMPERADORE *Stazione Zoologica Anton Dohrn* (*7*); COURTESY OF LUKE MANINOV HAMMOND (*8*); SOLEDAD DE OLMOS *Medical Research Institute Mercedes and Martin Ferreyra (INIMEC-CONICET–National University of Córdoba)* (*9*); IMAGE BY ELIZABETH JAMESON, WITH ASSISTANCE OF DEPARTMENT OF NEUROLOGY, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO (*10*)

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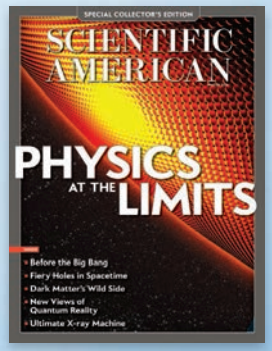
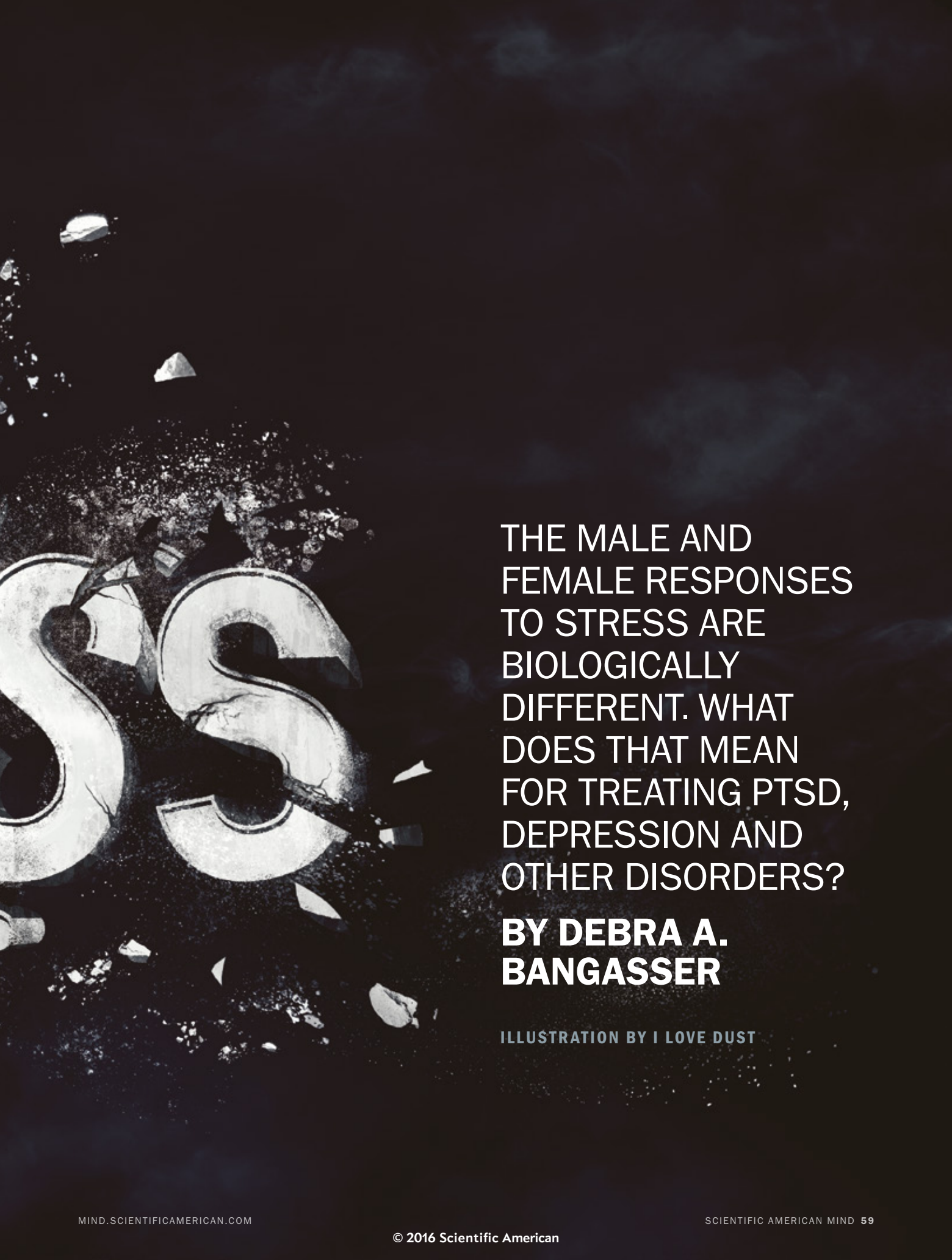




THE MALE AND FEMALE RESPONSES TO STRESS ARE BIOLOGICALLY DIFFERENT. WHAT DOES THAT MEAN FOR TREATING PTSD, DEPRESSION AND OTHER DISORDERS?

BY DEBRA A. BANGASSER

ILLUSTRATION BY I LOVE DUST

Think about the last time you felt stressed. Did your heart rate quicken? Did your breathing get shallow and fast? Maybe your muscles tensed, and you became more alert? The brain prompts all these physiological changes to help us survive in the face of a potentially life-threatening situation. But when this response is activated inappropriately or persistently, it can become dangerous. Indeed, research has linked uncontrolled stress to a wide range of health problems, from heart disease and diabetes to depression and post-traumatic stress disorder (PTSD).

Women are roughly twice as likely as men to suffer from stress-related psychiatric disorders, according to epidemiological analyses. The big question has always been: Why? Some experts argue that cultural factors are at least partly responsible. For instance, women may be more willing than men to seek help for mental illness, making their cases more likely to be counted. But new evidence from animal research suggests that biology may also play an important role. Scientists are uncovering telling differences in the ways that male and female brains react and adapt to stress.

This insight has been a long time coming. Historically, scientists studied male animals almost exclusively—even when investigating disorders that seem to occur more frequently in women. One reason is that many researchers feared that fluctuating ovarian hormones would complicate their studies, muddy their data, and create a need for more subjects or more time at greater expense. Recent investigations have discredited this line of reasoning—the data collected from female animals are no more variable than those from males—but the male bias in animal research has persisted nonetheless.

FAST FACTS
UNDER PRESSURE

1. Animal studies are revealing significant sex differences in stress responses, even at the most basic cellular level.
2. In female rodents, chronic stress produces faster, stronger effects than it does in males. If similar differences exist between men and women, it could explain why women are more often diagnosed with stress-related psychological disorders such as depression and PTSD.
3. New efforts to include both male and female animals in research studies may help scientists understand these differences better and lead to more effective, sex-specific treatments for people.

To address this issue, the National Institutes of Health, which funds much of the biomedical research in the U.S., has launched a new effort. Starting this year, the agency requires that scientists conducting animal studies include sex as a biological variable in their research by studying both male and female animals. As a result, researchers who study chronic stress stand a much better chance of understanding how it impacts the health of both sexes—work that could lead to more effective, sex-specific treatments for psychological disorders. In fact, some of the most promising new therapies under investigation—including oxytocin for anxiety and ketamine for depression—appear to have very different effects in females than in males.

Female Stress

The animal models scientists use to explore the effects of stress take many forms. Some researchers expose rodents to something stressful—perhaps a brief restraint or sound they have conditioned the animals to associate with a mild shock—for several days in a row. Others alter levels of stress-related chemicals, such as glucocorticoids or corticotropin-releasing factor (CRF), in the animals' brains via genetic engineering and other techniques. Regardless of the method, these manipulations seem to produce faster and stronger reactions in females. We are just beginning to understand why.

It turns out that the most basic cellular processes involved in the stress response differ between the sexes. For example, neuroscientist Georgia E. Hodes, working in Scott Russo's laboratory at the Icahn School of Medicine at Mount Sinai, recently conducted a study in which she and her colleagues stressed male and female mice over the course of

several weeks. They noticed that it took 21 days to increase anxiety and depressivelike behaviors in male mice but only six days to produce the same reaction in female mice. In search of an explanation, they looked to the nucleus accumbens, a brain region involved in seeking out rewarding and pleasurable activities. Disruption of normal brain signaling in this area is thought to contribute to anhedonia, or an inability to experience pleasure, which is a common symptom in depression and various other stress-related disorders.

Within the nucleus accumbens, Hodes identified sex differences in the regulation of a gene called *Dnmt3a* (*DNA methyltransferase 3a*). Following a six-day stressor period, it was expressed more in female mice than in males. This gene encodes an enzyme that alters a cell's DNA in such a way that it prevents other genes from being read and used to make proteins. To determine *Dnmt3a*'s role in chronic stress, Hodes removed the gene in the nucleus accumbens of female mice. Without it, the females became more resilient and responded more like male mice. These findings suggest that female mice experience an increase in *Dnmt3a* expression after only a short exposure to stress, which then blocks other proteins that promote stress resilience. Interestingly, researchers are developing drugs that inhibit Dnmt enzymes to treat certain cancers. Therefore, similar drugs may be helpful in treating stress-related disorders, particularly in women.

Changes in gene expression are not the only sex differences in the brain. When I was a postdoctoral fellow, my mentor, neuroscientist Rita Valentino of the Children's Hospital of Philadelphia, and I discovered sex differences in receptors that respond to CRF, a hormone that helps to kick-start the body's biochemical response to stress. Although there are CRF receptors in many brain regions, we focused on the locus coeruleus, a structure responsible for changing our levels of arousal from sleepy to fully awake. During a stressful event, CRF floods the locus coeruleus, where it binds to CRF receptors to keep an animal on high alert. Typically these receptors sit on the outside surface of brain cells, waiting for a CRF signal. As CRF levels rise, however, the receptors migrate from the cell membrane to its interior, effectively going off-line. This process is thought to protect brain cells from becoming overactivated.

We discovered that in male rodents, CRF receptors withdrew inside neurons after exposure to a standard stressor. They also withdrew in male rodents genetically modified to overexpress CRF. In female rodents, though, the receptors lingered on the cell membrane, where they could remain responsive to high CRF levels. The results suggest that CRF may increase arousal and alertness more in females than in males. In some situations, this difference may actually be adaptive: it can be a good thing to stay fully switched on during a stressful occurrence. But overactivation of this system can also

GETTY IMAGES

How **Scared** Is That Rat?

Researchers who study stress in humans can ask their subjects how they feel: Are you stressed, fearful, anxious or depressed? That doesn't work with a rat. Instead my colleagues and I have to try to evaluate a rodent's emotional response to stress indirectly—which means we take careful note of changes in behavior that are thought to reflect fear, anxiety or even aspects of depression. Unfortunately, these behavioral cues were all validated in males and do not necessarily capture signs of stress and fear in females.

In 2015 neuroscientist Rebecca Shansky and her graduate student Tina M. Gruene of Northeastern University demonstrated that female and male rats have different ways of expressing learned fear. In their experiments, they followed a standard fear-conditioning procedure, teaching rodents to be afraid of a tone by pairing it repeatedly with a mild electric shock to the paw. To gauge how well a rat learns the association, researchers typically measure how much it stops moving (except for breathing) when it hears the tone. The more the rat freezes, the more fearful it is, and the better it has learned—or so the logic goes. But when scientists began testing female rats in the same way, they found that they did not freeze as much as the males did.

Did that mean the females did not learn as well? As it turned out, that does not seem to be the case. With careful observation, Shansky and Gruene noticed that after the conditioning, many female rats darted around their enclosure, perhaps trying to escape. When they considered darting as an indicator of fear, the apparent gap in learning ability disappeared. ***—D.A.B.***

THE AUTHOR

DEBRA A. BANGASSER is an assistant professor at Temple University, where she is also principal investigator of the Neuroendocrinology and Behavior Laboratory.

lead to hyperarousal, a disruptive state that, in humans, contributes to insomnia, impaired concentration and feeling inappropriately "on edge."

Patients with PTSD and depression can exhibit high levels of CRF and these symptoms of hyperarousal. So if similar sex differences are found with human CRF receptors, it could help explain why women are more likely to suffer from PTSD and depression. This variation may be hard to demonstrate, however. When human brains are being imaged, technical limitations make it difficult to detect molecular changes such as CRF receptor localization. But we have other reasons to believe that women, like female mice, may have a greater sensitivity to CRF: injecting it into the bloodstream causes a greater rise in stress hormones in women than in men.

The Impact of Hormones

Where do these differences come from? Emerging research points to the different complement of genes males and females are born with—as well as hormonal surges in the womb and during puberty, both of which can permanently alter the developing brain. Additionally, fluctuating levels of testosterone, estrogens and progesterone can modulate brain function in adults. In my laboratory at Temple University, we are beginning to assess the role that these circulating hormones play in regulating rodents' behavioral responses to high levels of CRF, by looking at compulsive grooming.

When a rat compulsively licks its own fur, sometimes to the point of causing baldness, it is thought to reflect a state of high anxiety. The compulsive grooming may be a form of self-soothing. We found that when we injected CRF into rats to induce stress, females engaged in more compulsive grooming than males did. Moreover, the amount of grooming changed over the course of a female's estrous cycle, which is similar to the human menstrual cycle but lasts only four to five days. At the phase of the cycle when ovarian hormones—including estrogens and progesterone—peaked, CRF triggered even more compulsive grooming, suggesting that the hormones somehow amplify CRF's effects.

Behavioral responses such as grooming draw on many brain regions. So in trying to account for the grooming differences between the male and female rats, a graduate student in my lab, Kimberly Wiersielis, speculated that CRF might activate different circuits in their brains. To test this idea, she examined brain slices for cFos, a protein expressed only when brain cells are switched on. Then we statistically compared cell-activation patterns. Our analysis revealed that in both sexes CRF activated diverse brain regions but that the patterns were different—and especially so between males and females at the point during estrous when females have the highest levels of estrogens and progesterone.

A Sex-Based Rx

These sex differences are not minor. As we search for better remedies for stress-related psychiatric conditions, it is vital that we take them into consideration. To date, potential therapies are most often screened in male rodents. But the same compounds can have very different effects in females. For example, neuroscientist Brian Trainor and his graduate student Michael Q. Steinman of the University of California, Davis, tested one putative therapy, oxytocin, in both male and female mice. Because this hormone promotes social bonding in mammals, scientists have speculated that administering it to people in the form of a nose spray might reduce social anxiety and avoidance, as well as improve deficits in processing social cues, a problem seen in some patients with stress-related psychiatric disorders. Trainor's group found that intranasal oxytocin did indeed reduce anxiety in male mice, but it made female mice even more anxious under certain conditions. We need to make sure that oxy-

A Heavier Toll for Women

Women are more likely than men to be diagnosed with a psychiatric disorder related to stress, with the exception of substance abuse. This discrepancy may be partly because of social factors, such as male reluctance to seek help. But it probably also reflects biological differences in how male and female brains respond to stress.

Lifetime Prevalence (percent)

DISORDER	FEMALE	MALE
Major depression	**20.2**	**13.2**
Migraine	**18.2**	**6.5**
Irritable bowel syndrome	**14.5**	**7.7**
Insomnia	**12.9**	**6.2**
PTSD	**9.7**	**3.6**
Alcohol abuse	**7.5**	**19.6**
Generalized anxiety	**7.1**	**4.2**
Panic	**6.2**	**3.1**
Drug abuse	**4.8**	**11.6**

SOURCE: "SEX DIFFERENCES IN STRESS-RELATED PSYCHIATRIC DISORDERS: NEUROBIOLOGICAL PERSPECTIVES," BY DEBRA A. BANGASSER AND RITA J. VALENTINO, IN *FRONTIERS IN NEUROENDOCRINOLOGY*, VOL. 35, NO. 3; AUGUST 2014

OUR PAST RELIANCE ON MALE ANIMALS IN DRUG DEVELOPMENT STUDIES MAY EXPLAIN, AT LEAST IN PART, WHY WOMEN REPORT MORE ADVERSE DRUG REACTIONS THAN MEN DO.

tocin sprays will not cause similar adverse side effects in women.

Ketamine provides another example. This medication, normally used as an anesthetic, blocks the *N*-methyl-D-aspartate receptor, a protein that can regulate many processes, including aspects of the stress response. It has generated a lot of excitement as a potential therapy for depression because, unlike traditional antidepressants that can take weeks to provide any benefit, low doses of ketamine reduce symptoms fast, sometimes after a single infusion. Unfortunately, high doses of ketamine can induce delirium, hallucinations and an "out of body" experience (which is why it is also a popular recreational drug).

Researchers have been investigating ketamine in male animals to develop more targeted therapies for depression. In 2013, though, neuroscientist Mohamed Kabbaj and his graduate student Nicole Carrier of the Florida State University College of Medicine also tested ketamine in female rats. They found that it took less ketamine to relieve depressionlike symptoms in the females and that it was not just a matter of differences in body mass. Instead a different biological mechanism seemed to be at work. If these same differences exist in humans, researchers working on new drugs with ketaminelike properties may need to develop separate therapies for men and women. Currently researchers are evaluating ketamine for its long-term safety and effectiveness, and these studies may well reveal that, like female rats, women should receive a lower dose.

We do not know why males and females would have evolved different biological responses to stress. To speculate, one possibility is that a female animal protecting vulnerable young might be well served by being able to maintain a heightened state of alert and awareness of her surroundings—as would her babies. That advantage might trump the downstream risks associated with increased stress sensitivity, such as greater vulnerability to depression and anxiety disorders. Studies are needed, however, to investigate this idea.

As we commit to including female animals in research, we stand to learn more not only about disorders that are more common in women but also about conditions that are more often diagnosed in men, such as autism and attention-deficit/hyperactivity disorder. In this case, looking at brain differences in females might reveal factors that confer greater resilience. Better-targeted treatments for both sexes could follow.

It is becoming increasingly clear that the traditional approach of only studying male animals is flawed. In fact, our past reliance on male animals in drug development studies may explain, at least in part, why women report more adverse drug reactions than men do. The practice may also have kept drugs that would be highly effective in females from ever making it to market. The good news is that thanks to new efforts that promote the study of both male and female animals, all that is about to change. **M**

MORE TO EXPLORE

- **Sex Differences in the Antidepressant-like Effects of Ketamine.** N. Carrier and M. Kabbaj in *Neuropharmacology,* Vol. 70, pages 27–34; July 2013.
- **Sexually Divergent Expression of Active and Passive Conditioned Fear Responses in Rats.** Tina M. Gruene et al. in eLife, Vol. 4, Article No. e11352; November 14, 2015.
- **Sex Differences in Nucleus Accumbens Transcriptome Profiles Associated with Susceptibility versus Resilience to Subchronic Variable Stress.** Georgia E. Hodes et al. in *Journal of Neuroscience,* Vol. 35, No. 50, pages 16,362–16,376; December 16, 2015.
- **Sex-Specific Effects of Stress on Oxytocin Neurons Correspond with Responses to Intranasal Oxytocin.** M. Q. Steinman et al. in *Biological Psychiatry,* Vol. 80, No. 5, pages 406–414; October 19, 2016.

From Our Archives

- **His Brain, Her Brain.** Larry Cahill; *Scientific American,* October 2012.

HEAR THE VIOLET, TASTE THE VELVET

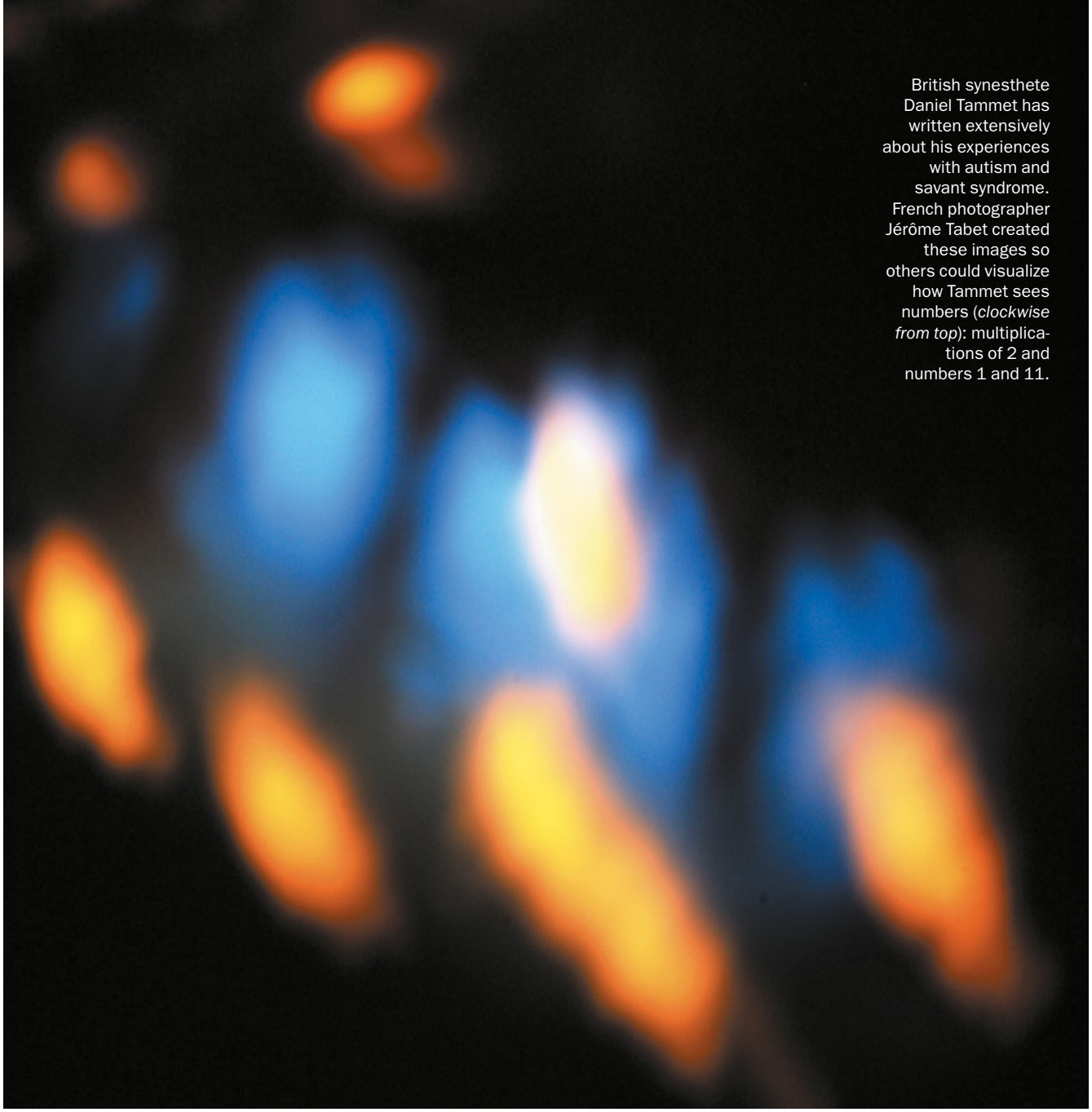
Research is unwinding the physiological basis of synesthesia, finding links to migraine, autism and other conditions that suggest a role for the immune system By Marta Zaraska

During a rehearsal one day in 1842, Hungarian composer Franz Liszt was less than thrilled with the performance of the Weimar orchestra, which he directed. "Gentlemen, a little bluer, if you please!" he exclaimed, astounding the musicians. How on earth does one play bluer? Similar requests followed, according to a report in the musical periodical *Neue Berliner Musikzeitung*. Liszt demanded the orchestra not to go "so rose," because the music was instead a "deep violet."

Unlike most—if not all—of the orchestra players, Liszt was a synesthete, someone for whom the stimulation of one sense causes automatic and unusual experiences in another sense. For people like Liszt, sound-to-color synesthetes, musical notes or even the sound of a door slamming or a car honking can trigger seeing colors. Russian composer Nikolay Rimsky-Korsakov famously believed A major to be clear pink and B major a "gloomy dark blue with a steel shine."

How common synesthesia may be remains a matter of debate. Older estimates put the prevalence at a mere one in 100,000 people, yet more recent work suggests it is far more common—possibly affecting one in 23 people. One reason for the uncertainty is that some experts define the condition more narrowly than others. Beyond sound-to-color synesthesia, researchers have counted more than 60 varieties, and some say there may be 150 kinds.

The most common by far is grapheme-color synesthesia, affecting roughly one in 100 people, which involves experiencing letters as having colors. Rus-



British synesthete Daniel Tammet has written extensively about his experiences with autism and savant syndrome. French photographer Jérôme Tabet created these images so others could visualize how Tammet sees numbers (*clockwise from top*): multiplications of 2 and numbers 1 and 11.

JÉRÔME TABET

sian-born writer Vladimir Nabokov, for example, saw the letter K as having the color of huckleberry, and S to him was "a curious mixture of azure and mother-of-pearl." (The specific color associated with each letter varies from one synesthete to the next, although many see A as red.) Other people experience smells as having sounds or days of the week as possessing different flavors. Sean Day, synesthesia researcher and president of the International Association of Synaesthetes, Artists, and Scientists, says that for him beef tastes blue. Even rarer types include the sensation that numbers have personalities (for example, "4" was "demure" to one synesthete) or the experience that swimming styles evoke different colors (such as a red butterfly stroke).

Although scientists have been fascinated with synesthesia for at least two centuries, only in the past decade or so has there been an upsurge in research. The first major findings proved definitively that synesthetic experiences are real—something previous generations had debated. More recently, boosted by technological advances such as whole genome sequencing, scientists have begun to unravel the biological basis for synesthesia. As evidence from brain imaging, molecular biology and epidemiology comes together, scientists are focusing on a totally unexpected variable: the immune system.

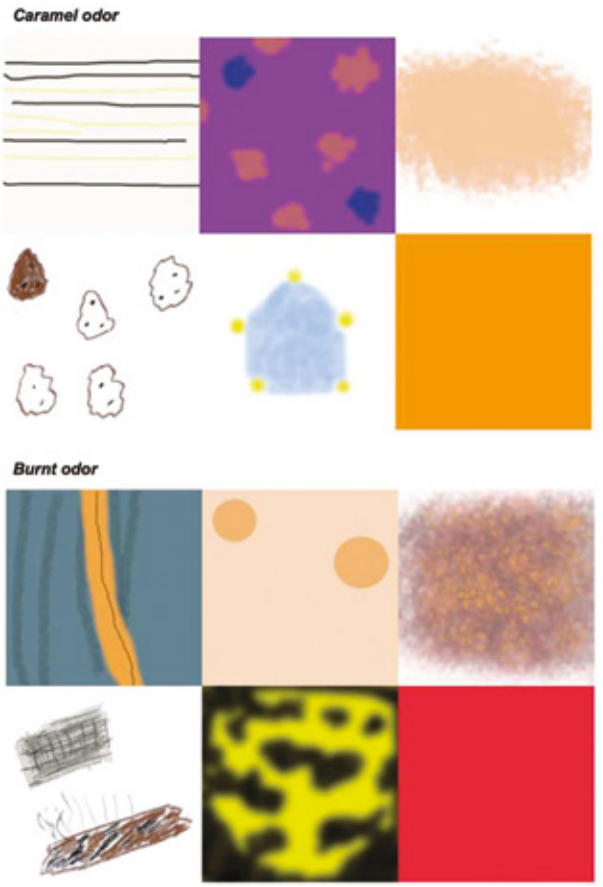
The Synesthetic Brain

Even a few decades ago synesthesia was not widely accepted as a neurological phenomenon. It could be verified only by self-report and was sufficiently rare that many people were dubious. For that reason, much early research focused on two questions: Was the experience real (as opposed to a creative mind's fancy)? And if so, what was happening during these strange sensations? Neuroimaging helped to answer both.

Using multiple techniques, researchers have discovered that the brain of a synesthete responds differently to sensory stimulation than a typical brain. For example, some scientists have employed magnetoencephalography (MEG), a technique in which patients sit with their head in a tubelike apparatus (similar in appearance to an old-fashioned salon hair dryer) to provide real-time insight into brain activity. In 2010 scientists at the University of California, San Diego, and Vanderbilt University used MEG to study the brains of Nabokov-like grapheme-color synesthetes who looked at white letters on a black background. The team found that an area of the brain called V4, a region of the visual cortex that responds when you see colors, becomes active a mere 110 milliseconds after a synesthete looks at colorless letters. This suggests that the experience of synesthesia is not just real but also automatic.

In a 2013 study, 20 grapheme-color synesthetes and 19 control subjects were asked to watch or listen to episodes of *Sesame Street,* a children's television show full of letters and numbers, while lying in a functional MRI machine. The results revealed that these synesthetes have greater cross activation between the areas of the brain responsible for letters and those responsible for colors. In other words, for synesthetes, neurons in these two areas are "talking" more with each other than in nonsynesthetes, such that simply hearing a *Sesame Street* character mention a letter (without actually seeing it) causes visual areas of the brain to light up on a scan.

The brains of synesthetes are also anatomically distinct. If you did a neuroimaging study of Liszt's or Rimsky-Korsakov's brain, you would likely find increased volume of both gray matter (made up largely of nerve cell bodies and glial cells) and white matter (the cells' wirelike axons that carry the brain's signals) in the areas involved in hearing and color. A 2013 MRI



In 2015 a team of researchers in Australia asked six synesthetes to illustrate the visual experiences they had in response to a caramel odor (*top*) or a burnt smell (*bottom*).

FROM "CHOCOLATE SMELLS PINK AND STRIPY: EXPLORING OLFACTORY-VISUAL SYNESTHESIA," BY ALEX RUSSELL ET AL., IN *COGNITIVE NEUROSCIENCE*, VOL. 6, NOS. 2–3; 2015

FAST FACTS

COLORFUL CONUNDRUMS

1. Neuroimaging reveals that the brain of a synesthete has unusual connectivity between regions and that stimulating one sense in these individuals spurs activity related to another sensation.
2. Various genes appear to contribute to a predisposition for the condition, several of which are known to influence connections in the brain.
3. Based on the unusually high prevalence of synesthesia among people with autism, irritable bowel syndrome, multiple sclerosis and migraine, a new hypothesis suggests that immune proteins play a part in the development of synesthesia.

study of 10 people with sound-to-color synesthesia and 10 nonsynesthetes found just that. Compared with the controls, the synesthetes had more white matter between visual and auditory areas of the brain, indicating greater connectivity between the two regions.

Other studies have shown more widespread changes—particularly increased gray matter—in the frontal and parietal lobes of synesthetes, which are considered higher-level brain regions involved in cognition. Given these findings, it is possible that people have a general predisposition to synesthesia rather than a propensity toward just one particular type, whether it is seeing the letter A in red or tasting blue in beef. And this predisposition may be linked to the unusual connectivity in a synesthete's brain—although it is hard to draw a causal conclusion. "It's not entirely clear whether having synesthesia causes altered neural pathways or whether altered neural pathways cause synesthesia," says Duncan Carmichael, a psychologist at the University of Sussex in England. "It's probably a bit of both."

> If you are a synesthete, as many as 40 percent of your close relatives are, too. Genetic and brain-imaging studies suggest the condition involves unusual neural connectivity.

Indeed, research confirms that synesthetic experiences are, to some extent, learned [*see box on page 69*]. "We first have to know that A is A and B is B, before we can actually have consistent color experiences with these letters," says psychologist Nicolas Rothen of the University of Bern in Switzerland. "I could very well imagine that there is a genetic basis that provides a threshold for how much learning needs to occur for someone to get these experiences. For some people it might be very easy to acquire synesthesia, and for other people it might be entirely impossible."

On a Blue Day

One hint that synesthesia's unusual neural architecture is partially inborn comes from genetics. If there is one synesthete in your family, as many as 40 percent of your first- and second-degree relatives most likely are synesthetes, too. What has been tricky to figure out, at least until recently, is how synesthesia gets inherited and which particular genes are responsible for the ability to, say, perceive the letter K as a huckleberry hue.

The good news is that as the costs of genome-wide studies go down, it becomes easier for researchers to explore the genetic basis of synesthesia. In 2009 a group of British and Italian scientists led by geneticist Julian Asher, then at the University of Oxford, published the first such study. The researchers took DNA samples from 196 synesthetes in 43 different families. Comparing genomes, they confirmed that synesthesia is indeed heritable but did not pinpoint one specific synesthesia gene. Instead Asher and his colleagues linked many different genes to synesthesia, bolstering the idea that some people may have what scientists call a "synesthesia genotype," a general predisposition stemming from multiple genetic characteristics.

Some of the genes that the researchers identified were found on chromosome 2. These areas were notable because they are also where you can find several genes involved in neural connectivity in the brain. A similar investigation, published in 2011 by researchers at the Baylor College of Medicine, the University of Alabama at Birmingham and the University of Texas Medical School at Houston, showed that genes associated with synesthesia may also be found on chromosome 16, in a region linked to abnormal neural connectivity. Taken together, the two studies suggest that the unusual brain connections of synesthesia most likely involve a genetic component.

In addition, the 2009 genome-wide analysis linked synesthesia to a variant on the long arm of chromosome 2, previously implicated in autism. That connection could help explain the famous case of Daniel Tammet, a 37-year-old British man who not only has been able to recite pi to 22,514 decimal places but also managed to learn conversational Icelandic in just one week. Tammet has both autism spectrum disorder and synesthesia. He sees numbers as having colors, sounds and textures. In his memoir *Born on a Blue Day,* he writes that number 1 is "a brilliant and bright white, like someone shining a flashlight into my eyes. Five is a clap of thunder or the sound of waves crashing against the rocks. Thirty-seven is lumpy like porridge, while 89 reminds me of falling snow."

Tammet's case was among the first to inspire scientists, such as Simon Baron-Cohen, a developmental psychopathologist at the University of Cambridge, to inquire into the possible links between autism and synesthesia. The conditions share a few resemblances: both are characterized by neural hyperconnectivity, and people with both conditions are more likely than the average individual to have perfect pitch (the ability to instantly name and recognize musical notes).

In 2013 Baron-Cohen and his colleagues found that in a sample of 164 adults with autism and 97 without, there were almost three times as many synesthetes among people with au-

THE AUTHOR

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tism as in the second group. Later that year a team of scientists, including neurobiologist Janina Neufeld, then at the University of Reading in England, had similar findings. The prevalence of grapheme-color synesthesia among those on the autism spectrum could be as much as 31 percent higher than in the general population. "If certain genes involved in local brain connectivity are different in a person, he or she might have an increased likelihood to develop both conditions," Neufeld says. She adds that for autistic people, who often have a strong drive to systemize things, synesthesia could help them "make sense of the world."

> In one study, there were almost three times as many synesthetes among individuals with autism as those without. Prevalence may also be higher among people with immune disorders.

Unfriendly Mrs. Monday

In 2008 a woman from Edinburgh participated in one of Carmichael's experiments on synesthesia. She had several variants, including sequence-personality synesthesia (in which one might feel, for example, that Mondays were female and unfriendly). During the study, she underwent an MRI scan, which was then examined by a radiologist. The results were troubling. She had white matter lesions suggestive of multiple sclerosis (MS).

In 2015 Carmichael and his colleagues published a review of various studies on synesthesia in which MS-like lesions had been detected. Admittedly, the overall number of cases was tiny—just three among 234 synesthetes. But that gives a prevalence of 1,282 in 100,000 people, which is nine times higher than what is usually found in the general population. It is possible that MS, which damages the myelin that insulates nerve fibers, could contribute to sensory changes that mimic synesthesia's effects.

MS is not the only malady linked to synesthesia. In 2012 scientists at the University of Manchester in England published a study of 200 patients with irritable bowel syndrome (IBS) and the same number of control subjects. It showed that 9.5 percent of IBS sufferers experienced synesthesia versus just 3 percent in the control group. One patient remembered attending a concert as a child and telling her mother afterward how much she liked the colored laser show that accompanied the music. The mother was baffled. There had been no laser display. The light show was a product of her daughter's synesthesia.

Some migraine sufferers also experience such colorful displays. The connection could be explained by the fact that both people with migraines and those with synesthesia often have what scientists call hyperexcitability of the visual cortex. If you stimulate their brain with a magnetic field by placing a special generator near their head, they will experience visual illusions.

A 2015 study, which analyzed 161 female synesthetes and 92 female nonsynesthetes, showed that migraine with aura (a painful headache preceded by symptoms such as light sensitivity or hallucinations) may be associated with certain types of synesthesia, such as those connected to touch, taste, emotion and personality. According to the study's lead author, Clare Jonas of the University of East London, the aura could be a type of synesthetic experience in itself: "One possibility is that you have some visual disturbance that most people don't have and your synesthetic response to it is a headache, so aura causes pain."

Inspired by such curious overlaps, Carmichael and Julia Simner, a psychologist at Sussex, have proposed an explanation for how synesthesia comes about. Autism, IBS, migraine and MS are all conditions in which immune system dysfunction plays a role. According to their "immune hypothesis," synesthesia may arise from a variation in immune-related genes, which in turn results in changes to the brain's connectivity.

Broadly speaking, immune system proteins have a different function in an adult than they do in a developing baby. In adults, they generally tag pathogens so that white blood cells can remove them. But in small children, some of these immune proteins tag brain synapses for removal instead. "When you are born, your brain is essentially like a big block of stone that needs to be sculpted. You have far more synapses and far more connections than you end up using," Carmichael explains. This abundance of connections sounds like a good thing—but that kind of brainpower comes at a cost, in this case, high-energy consumption. For the sake of efficiency, we have to lose a lot of connections that are not regularly used, a process known as synaptic pruning.

If the immune system proteins do not function properly and do not prune enough synapses, we are left with extra connectivity between brain regions, which could in turn lead to synesthesia. In fact, the two genome-wide studies pinpointed regions of chromosomes that also contain immune function genes.

Does that mean synesthetes should worry about developing migraine or immune disorders such as multiple sclerosis? "Not on the basis of the evidence we have now," Carmichael reassures. "Just like being a man or being a woman makes you more susceptible to certain medical conditions, being a synesthete might change your risk profile in terms of getting certain medical conditions—but whether this is true, it's too early to say."

Bern's Rothen, for one, believes that we need to see if large investigations, involving thousands of synesthetes, confirm the high prevalence of immune disorders among such people. "A lot of studies so far have been based on very small samples, so we need to be cautious," he says.

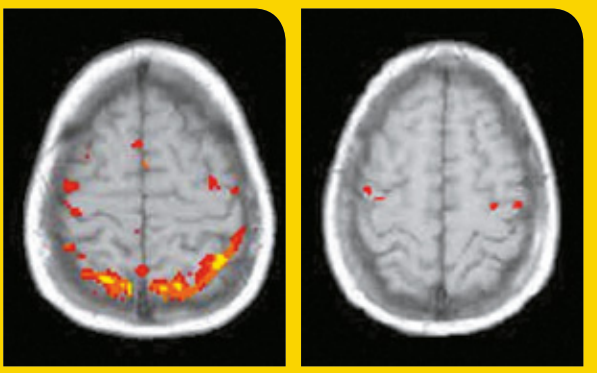
So, You Want to Be a Synesthete?

Tasting words, smelling shapes and other synesthetic experiences can have their advantages. The condition has long been linked to creativity—as the lists of famous artists, writers and musicians with synesthesia would suggest—and the strange sensory overlaps may also boost memory. All of which leads many nonsynesthetes to wonder whether they could learn to see sound and taste letters.

There are several "artificial" approaches to synesthesia—sensory deprivation or psychedelic drugs, for instance, are purported to achieve a similar effect—but in most "natural" cases there is clearly a genetic component. Still, learned experience plays an important role in establishing specific sensory associations. This fact can help explain why, for example, people who see letters in color often see A, a frequently used letter, in red, a common hue.

Some experiments suggest people can be trained to acquire synesthetic experiences. In 2014 psychologist Nicolas Rothen and his colleagues, all then at the University of Sussex in England, signed up 14 volunteers—who had no personal history of synesthesia—for an intensive training course in which they were taught 13 letter-color associations. After nine weeks the participants started seeing letters in color even outside the laboratory. But the results of other similar studies were mixed, with several failing to train people to experience any form of synesthesia.

In one case report, a nonsynesthete spent eight years mastering the art of cross-stitching, in which numbers signify the use of specific thread colors (for example, "3" means "red"). When the nonsynesthete's performance on connecting colors with numbers was compared with that of a synesthete, the two were basically indistinguishable. But there was a catch. During functional MRI tests, their brains lit up very differently, suggesting that the experience of the synesthete was unlike that of the trained person. What is unique to synesthesia, the authors conclude, are "photisms"—involuntary, hallucination-like sensations of light or color.



Cross-stitchers learn to link numbers and colors much like a grapheme-color synesthete. But an fMRI scan conducted while both types of subjects added numbers showed that a synesthete (*left*) had more activity in visual areas than a stitcher did (*right*).

In 2014 Rothen and psychologist Beat Meier of the University of Bern in Switzerland reviewed the seven synesthesia-training studies published to date. They concluded that even if we can train some aspects of synesthesia so some people can mimic these sensations, the true experience probably remains out of reach for most of us. —*M.Z.*

FROM "DISSOCIATING SEMANTIC AND PERCEPTUAL COMPONENTS OF SYNAESTHESIA: BEHAVIOURAL AND FUNCTIONAL NEUROANATOMICAL INVESTIGATIONS," BY LORIN J. ELIAS ET AL., IN *COGNITIVE BRAIN RESEARCH*, VOL. 16, NO. 2: APRIL 2003

Matters of Immunity

The immune hypothesis fits into a larger revolution in neuroscience. For decades scientists saw the brain and immune system as distinctly separate entities. Thanks to the powerful blood-brain barrier, the thinking went, the two could not interact. But increasingly, scientists are tearing down the old divide. The central nervous system is not exempt from immune effects. Instead immune proteins play a part in brain development and maintenance.

Even if synesthesia is a by-product of immune-related genes underpruning the brain, it is a positive by-product. Rothen has found a link with a specific profile of enhanced memory, for example, and other studies show synesthetes can be more creative and have improved color perception.

From an evolutionary perspective, all of this shows how synesthesia may have come in handy over the generations. If you were picking berries in a Paleolithic forest, being able to differentiate one type of fruit from another by their shade may have been a matter of life and death—and detecting extrasensory cues would be advantageous. Nowadays, Neufeld says, synesthetic experiences could help us "memorize things like color coding a pin number." By that logic, "brilliant white of a flashlight, thunderclap, lumpy porridge" could be the buzzer code for a friend's front door and "huckleberry, mother-of-pearl, vulcanized rubber" might serve as the perfect password. M

MORE TO EXPLORE

- **Some Demographic and Socio-cultural Aspects of Synesthesia.** Sean Day in *Synesthesia: Perspectives from Cognitive Neuroscience.* Edited by Lynn C. Robertson and Noam Sagiv. Oxford University Press, 2004.
- Daniel Tammet's 2011 TED talk on "Different Ways of Knowing": **www.youtube.com/watch?v=Pzd7ReqiQnE**
- **Developing Synaesthesia.** Edited by Nicolas Rothen, Julia Simner and Beat Meier. Frontiers in Human Neuroscience, July 2015.
- The Synesthesia Battery: **www.synesthete.org**

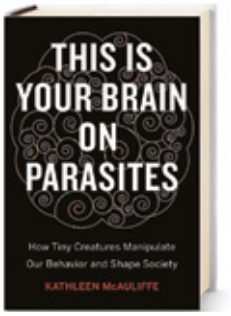
From Our Archives

- **Hearing Colors, Tasting Shapes.** Vilayanur S. Ramachandran and Edward M. Hubbard; *Scientific American,* May 2003.
- **Edges of Perception.** Ariel Bleicher; March/April 2012.

STRANGER THAN FICTION

This Is Your Brain on Parasites: How Tiny Creatures Manipulate Our Behavior and Shape Society

by Kathleen McAuliffe. Houghton Mifflin Harcourt, 2016 ($27; 288 pages)



Suicidal zombie insects, a wild-eyed scientist from Eastern Europe, blood-sucking and mind control. These are normally the stuff of vampire fiction, but they also loom large in neuroparasitology, the study of how parasites manipulate the behavior of their hosts. In *This Is Your Brain on Parasites,* science writer McAuliffe vividly delves into this burgeoning field, weaving in stories that are fascinating—and full of the kind of factoids you can't wait to share: Did you know that there's a tiny parasite that tricks crickets into drowning themselves so it can get into the water and lay eggs? Or a bug that makes rats run kamikaze right into cats' mouths?

As riveting as such trivia are, the book could prove challenging for the faint of heart (or weak of stomach, like this reviewer). There are moments of pure nature-channel gore, such as when McAuliffe delineates the life cycle of a guinea worm, a parasite that migrates from a human's intestinal muscle through the tissues of the body all the way to the lower limbs or sole of the foot where it—no, that's enough. Equally unnerving is the underlying existential question McAuliffe poses: Are some teeny creatures directing the behavior of bigger animals, including *us?* As she writes, the concept of such puppetry evokes "the horror of losing control."

Some of the most enjoyable parts in this book—for me, at least—come when McAuliffe takes a break from the bugs and biology to introduce some of the quirky scientists who study parasitic manipulation. Her writing is so rich and the interviews so sharp that you feel like you've met her subjects personally—and can't help but feel their passion for the work. These scenes also serve up a rare glimpse into the inner workings of a research lab and life as an academic. Take, for example, the French researcher who stole away during a romantic interlude with his wife to look for parasite-infected zombie crickets by their resort's pool (which he found).

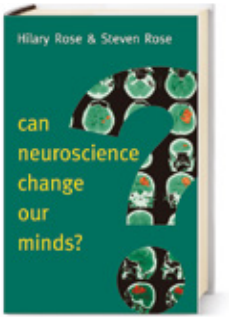
The first and best half of the book focuses on animal research. McAuliffe loses some of her scientific footing later on when she takes the leap from crickets and rats to people. For example, some interesting work has found that, compared with mentally healthy individuals, those with schizophrenia are more likely to carry antibodies for *Toxoplasma gondii,* a parasite commonly found in cat feces. But in general, the data on human neuroparasitology are too new, and too thin, to build a compelling case. Because parasites seem less likely to control mammals than insects, fish and crustaceans, McAuliffe explores their possible indirect effects—such as how our desire to avoid them may make some societies more fearful of outsiders and more focused on the greater good. What I grew to love, though, is that even in these weaker moments, she makes a point of quoting people who disagree with her.

Overall, McAuliffe has crafted an engaging narrative that, despite the grislier bits, kept drawing me in. In the same way that a good biography captures the essence of a person—his or her quirks, mistakes and triumphs—this book exposes the no longer secret lives of parasites. "Nature is full of ghastly and glorious surprises," McAuliffe writes—and her book is, too. *—Sunny Sea Gold*

NEUROHYPE

Can Neuroscience Change Our Minds?

by Hilary Rose and Steven Rose. Polity, 2016 ($45; 176 pages)



Neuroscience has gained mega-science status in recent years, with massive funding in the U.S. and the U.K. and major new initiatives under way in Japan and China. But just how advanced is neuroscience? Not very, according to some experts.

Almost 30 years ago, in *Blaming the Brain,* neuroscientist Elliot Valenstein argued that drug companies spawned the myth that brain science had discovered the causes of depression and anxiety. Both disorders remain mysterious to this day, however. Big pharma has few new drugs in the pipeline to treat them, and depression is increasing worldwide. In 1999 philosopher John T. Bruer said it was premature to use the little we understood about the brain as a guide for improving education or child rearing. And a 2006 essay by legal scholar Stephen Morse warned about the "brain overclaim syndrome"—or the tendency for experts in multiple fields, even judges, to conclude we understand much more about the brain than we actually do.

In this new book, Hilary Rose, an emerita professor of social policy at the University of Bradford, and Steven Rose, an emeritus professor of neuroscience at the Open University, both based in England, shine a critical light once again on glitzy neuroscience. The field, they say, is no closer to serving as a legitimate guide to education. Still, that has not stopped neuroscience from insinuating itself into classrooms worldwide in the form of teacher-training programs, computer applications and curriculum changes—not one of which is based on actual knowledge for the simple reason that we lack even "fundamental principles" of how the brain works, they write. We still do not even have a "theory of the brain."

Meanwhile the influence of neuroscience on education continues to mushroom, thanks to "opportunistic marketing" and promises that cannot be kept and even, in one prominent case, the fraudulent use of misleading false-color images of brain scans. A large, brightly colored image was said to demonstrate that early intervention programs with children produced healthy brains, whereas a small, dull scan was said to show how the failure to intervene produced sickly brains.

We are learning things from the brain sciences that might eventually help us repair damaged brains and understand mental illness, the authors say, but the frenzied, money-and-media-driven application of neuroscience from "neuroeducation" to "neuroeconomics" is premature. The solutions to the challenges we face are still social and behavioral, and neuroscience is distracting us from tackling the big variables, such as nutrition, inequality and poverty. "It's not necessary to understand the workings of the brain," they conclude, "to know that precariously housed, underfed children find it hard to study and learn."

This book is a bold, forthright and courageous commentary on looming cultural trends—a true tour de force. *—Robert Epstein*

Q&A with Alex Soojung-Kim Pang

Why is a rested brain more creative?

In his new book **Rest: Why You Get More Done When You Work Less** (Basic Books, 2016; 320 pages), Alex Soojung-Kim Pang argues that respite is an essential component of both productivity and creativity. Pang, a senior consultant at Strategic Business Insights and a visiting scholar at Stanford University, draws on biographical accounts and psychological studies to make his case, exploring the benefits of sleep, naps, play, sabbaticals and exercise. He answered questions from contributing editor Ferris Jabr. The full interview can be found online at www.ScientificAmerican.com/pang. An edited transcript follows.

What was the inspiration for the book?

It got started when I noticed a paradox in the lives of some really creative people: people like Charles Darwin, Stephen King, Maya Angelou, who are obsessed with their work. But when you look at how many hours a day they spent working, it's a surprisingly small number. For someone living in Silicon Valley and growing up in an era that assumes overwork is the norm, the idea that you could go in the opposite direction and yet still do really amazing stuff was really compelling. I started to think that maybe the secret had to do not just with how they work or their innate intelligence but also with the way they rested.

What I found is a community of people, including scientists and artists and authors, who follow this pattern of working very intensively a few hours a day and then resting deliberately in various ways. Rest is something we all know how to do naturally, but it's also something we can treat as a skill.

How have you come to define rest, and what are some of the biggest misconceptions about it?

What I mean by rest is engaging in restorative activity. It's not necessarily completely passive for one thing. We tend to think of rest as putting your feet up, and you've got the margarita and you're binge watching *Orange Is the New Black*. For people in my study, their idea of rest was more vigorous than our idea of exercise. These are people who go on long walks covering 15 or 20 miles in a day or climb mountains on vacation. For them, restful activities were often vigorous and mentally engaging, but they experienced them as restorative because they offered a complete break from their normal working lives.

What is the brain doing when we are at rest?

The critical thing to recognize is that when we are letting our minds wander, when our minds don't have any particular thing they have to focus on, our brains are pretty darn active. When you do things like go for a long walk, your subconscious mind keeps working on problems. The experience of having the mind slightly relaxed allows it to explore different combinations of ideas, to test out different solutions. And then once it has arrived at one that looks promising—that is what pops into your head as an aha! moment. The people I looked at are able to construct daily schedules that allow them to draw on that process in little increments.

What exactly is the form of rest known as deep play, and why is it beneficial?

It offers similar psychological rewards to work but in a very different medium or context. Winston Churchill took on painting during the First World War. He talks about it in a book called *Painting as a Pastime* as being very much like political argument—it requires the same kind of boldness and decisiveness; you literally have to have a clear vision of what is in front of you and what you want to achieve. At the same time the materials you are using are completely different, and the way you are using brush and paint allow you to put your cares aside. Over and over again people choose hobbies that they describe as being like their professional disciplines but also totally different.

KRISTIAN KETTNER (*Pang*); © ISTOCK.COM (*icon*)

ROUNDUP

New books tackle the science behind two intriguing questions:
What makes us really us?
Why do we swear?

Can you undergo such extensive augmentation that you almost become another person? Some celebrities—take Michael Jackson, for example—have altered their appearance so significantly that they no longer look like themselves. But in **Beyond Human: How Cutting-Edge Science Is Extending Our Lives** (Thomas Dunne Books, 2016; 304 pages), science writer Eve Herold goes a step further and examines medical innovations emerging in robotics, genetics and nanotechnology that promise to enhance our bodies and minds. As Herold investigates these technologies, she raises important ethical questions about what these potential feats of engineering may mean for, or do to, our humanity.

People curse for a variety of reasons—to express anger, make a joke or emphasize their point. But does cursing really serve any notable purpose? In **What the F: What Swearing Reveals about Our Language, Our Brains, and Ourselves** (Basic Books, 2016; 288 pages), cognitive scientist Benjamin K. Bergen researches the science of expletives to uncover the real reasons we swear and the influence four-letter words can have. Overall, Bergen suggests that our use of profanity may provide new insights into how our brain works, how we process language and how we communicate with others. *—Victoria Stern*

Why don't figure skaters get dizzy when they spin?

—**Anonymous** via e-mail

Amir Kheradmand, an assistant professor of neurology at Johns Hopkins Hospital, answers:

When we spin—on an amusement park ride or the dance floor—we often become disoriented, even dizzy. So how do professional athletes, particularly figure skaters who spin at incredible speeds, avoid losing their balance?

The short answer is training, but to really grasp why figure skaters can twirl without getting dizzy requires an understanding of the vestibular system, the apparatus in our inner ear that helps to keep us upright. This system contains special sensory nerve cells that can detect the speed and direction at which our head moves. These sensors are tightly coupled with our eye movements and with our perception of our body's position and motion through space. For instance, if we rotate our head to the right while our eyes remain focused on an object straight ahead, our eyes naturally move to the left at the same speed. This involuntary response allows us to stay focused on a stationary object.

> "Skaters, dancers and other athletes learn to "spot" while they spin. The technique may teach their brain how to suppress dizzy signals at their source, the inner ear."

Spinning is more complicated. When we move our head during a spin, our eyes start to move in the opposite direction but reach their limit before our head completes a full 360-degree turn. So our eyes flick back to a new starting position midspin, and the motion repeats as we rotate. When our head rotation triggers this automatic, repetitive eye movement, called nystagmus, we get dizzy.

Skaters suppress the dizziness by learning how to counteract nystagmus with another type of eye movement, called optokinetic nystagmus. Optokinetic nystagmus occurs in the opposite direction of the nystagmus and allows us to track a moving object—such as a train whizzing by—with our eyes while our head remains in place. As the first few cars of the train move out of view, our eyes jump back to their initial position to follow the next few, and the motion repeats. Skaters can train themselves to engage this opposing eye movement when they rotate to offset the nystagmus and keep the world from spinning.

Professional athletes employ a variety of other strategies to prevent dizziness, including maintaining a uniform speed. The sensors in our vestibular system can detect only changes in speed, so they fail to sense rotation that takes place at a steady pace. If athletes can manage their speed, they encounter dizziness only while they accelerate into and slow down out of a spin.

Ballet dancers employ another technique they call spotting. As they pirouette, they keep their body moving at a fairly constant speed but try to fix their gaze on one "spot," varying the speed at which they rotate their head. They hold it in place and then quickly whip it around at the end of each turn, minimizing the time their head is rotating and limiting any nystagmus. Learning to spot may offer ballet dancers an even broader benefit: a 2013 study suggests that the training might teach their brain how to suppress dizzy signals at their origin, the inner ear.

Despite these tricks, figure skaters and dancers still lose their balance sometimes, but here, too, intense practice comes in handy. If they rehearse and master graceful movements at the end of a spin, it can afford them the chance to recover after a brief dizzy spell.

Do animals recognize themselves?

—**Jay Jacobus** via e-mail

Marc Bekoff, professor emeritus of ecology and evolutionary biology at the University of Colorado Boulder, replies:

Do animals really know who they are? Experts have been puzzling over this intriguing question for decades, and the responses vary depending on whom you ask and how he or she defines self-awareness.

For years the litmus test was the so-called red spot test, developed by psychologist Gordon Gallup. A researcher

JAMIE CARROLL ©iStock.com

Are lefties physically or psychologically vulnerable?

—**Kevin McElroy** via e-mail

Stephen Christman, a professor of psychology at the University of Toledo, responds:

For much of its history, the field of neuropsychology strived to understand what was wrong with the human species' left-handed minority. This effort was eventually abandoned after two key insights emerged. First, experts realized that handedness has a genetic basis, and any attempts to change it can have deleterious developmental consequences. Second, we learned that left-handers have remained a stable 10 to 15 percent of the human population for thousands of years: if lefties were truly weaker in some way, their numbers would have dwindled over time.

Still, people continue to question whether lefties are more vulnerable to physical and psychological maladies, despite only shaky evidence to support such claims. A well-publicized study in the early 1990s, for instance, reported that lefties had shorter life spans than righties, but those results have since been discredited. Subsequent research found no meaningful differences in mortality rates.

Likewise, very little evidence indicates that lefties are more likely to develop physical ailments. Some highly speculative research suggests that left-handers may be at a greater risk for restless legs syndrome and asthma, but other investigations report that left-handers face a lower risk for chronic obstructive pulmonary disease and pneumonia. Some researchers have proposed a tenuous association between handedness and the risk of schizophrenia as well as creative thinking. Studies suggest that significantly fewer people who consistently use their right hand develop schizophrenia, compared with left- or inconsistent-handers, who use their nondominant hand for common activities. But this observation lacks a causal explanation.

Because most equipment is built for right-handers, it is possible that left-handers are more prone to physical injuries at work or accidents while driving. Studies also show, though, that left-handed professional athletes may have an advantage over their right-handed peers because their movements are less predictable. In summary, handedness may influence certain behaviors or risks for specific disorders, but the evidence to date does not definitively support or convincingly account for these links.

applies an odorless red spot to a sedated animal's forehead and then watches what happens when, fully awake, the animal confronts its image in a mirror. If it moves its paw toward the spot, the assumption is that it recognizes itself and has some degree of self-awareness.

But actually the red spot test is far too limited to reach this conclusion. First, it depends on animals knowing that mirrors create reflections—which they may not understand without previous experience. Second, and perhaps more problematic, many animals do not know what they look like; they recognize only what they smell or sound like. For instance, dogs and wolves depend heavily on olfactory cues, more so than visual ones, to navigate the world. In what I called the "yellow snow" experiments, I discovered that my dog, Jethro, could recognize his own urine and responded differently to the smell of his urine compared with that of other dogs. Animals such as Jethro may fail the red dot test but still possess some sense of self or ownership over their body and smells.

The legendary naturalist Charles Darwin believed that humans are not the only self-aware beings. In his theory of evolutionary continuity, he asserted that the differences among species come in degree rather than kind. So if humans display self-awareness, other animals most likely exhibit some form of this trait as well. In my own extensive work observing wild and domestic animals, I have indeed found that many exhibit different levels of self-awareness.

Being self-aware does not necessarily translate into a sense of what I call "I-ness." When an animal sees its reflection, for instance, it may not understand "That's me!" in the same way as a human would, but it may know that its body is its own and does not belong to someone else. Examples of this type of self-knowledge abound. Many animals know where their body is in space when they run, jump or navigate as a hunting pack or a migrating flock. Animals may also display ownership over *their* food, territory, family and body parts.

Although there is no easy answer to the question of self-awareness in animals, this line of inquiry leads to some fascinating insights into who animals are, what they know and how they feel. We may not grasp the extent of their self-consciousness, but I believe that an animal's awareness of its body and property ultimately equates to a sense of self. M

Do you have a question about the brain you would like an expert to answer?

Send it to MindEditors@sciam.com

1 ADDED VALUE

Each letter represents a number. The sums of each row and all but one column are given. Supply the missing total.

A	A	B	C	13
B	B	C	D	9
B	A	C	D	10
C	C	D	D	6
12	13	8	?	

2 DATING GAME

Follow the pattern to fill in the day of the month.

May 5

October 11

March 9

April ?

3 FAMILY TIES

Pat organized a party for her mother-in-law. She invited her mother-in-law's only daughter's only daughter's husband's only son. How is he related to Pat?

4 HIDDEN TRAITS

What do the following four words have in common? (Hint: The similarity has nothing to do with the number of letters, vowels, consonants or syllables they contain.)

SNIPS RACQUET ABACK CARTON

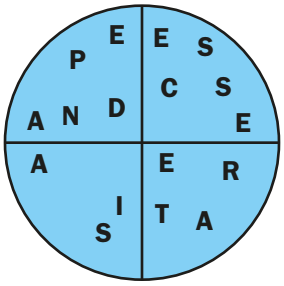
5 WAY WITH WORDS

Uncover the comment coiled in the grid below, starting with an "H" and then moving to an adjacent letter in any direction. Letters can be used only once.

T	I	S	A	L	X
H	G	Y	A	W	Y
S	I	S	T	W	T
D	N	T	N	E	N
H	I	Y	T	W	E

6 MISSING LETTER

Find the letter that completes the scrambled words in each quadrant at the right.



7 NEXT UP

Figure out the number that completes the sequence below.

3 7 15 31 ? 127

8 SETS OF SUMS

There are four sets of three three-digit numbers in which no two digits are the same and the first two numbers add up to 459. One such set appears below. Can you find the other three? (You may not transpose the top and bottom lines.)

176 ? ? ?
+283
459

9 ANAGRAM IT

Rearrange these 16 letters to make a four-word phrase meaning "absolutely lovely."

A A C E E I P P R R S T T T U Y

10 SCRAMBLED LETTERS

How many unusual English words can you make using the letters below, once each?

A G O R T

Answers

1. 5. (A = 4, B = 3, C = 2, D = 1.)
2. 8. (Make each consonant equal 2 and each vowel equal 1 and sum the letters of the month.)
3. Her mother-in-law's only daughter's only daughter is Pat's niece. The niece's husband's son is Pat's great-nephew.
4. Each contains a three-letter word spelled backward (PIN, CAR, CAB, NOT).
5. HINDSIGHT IS ALWAYS TWENTY-TWENTY.
6. The missing letter is "X" (EXCESS, EXTRA, AXIS, EXPAND).
7. 63. (To continue the sequence, multiply each number by 2, then add 1.)
8. 183 + 276 = 459, 186 + 273 = 459, 173 + 286 = 459.
9. PRETTY AS A PICTURE.
10. Two. ARGOT and GROAT.

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SCIENTIFIC AMERICAN MIND

Finding Her Nerve

BY DWAYNE GODWIN & JORGE CHAM

RITA LEVI-MONTALCINI WAS BORN IN TURIN, ITALY, IN 1909.

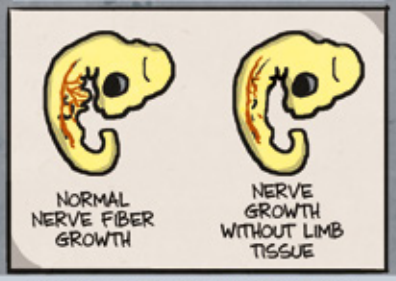
DESPITE EXPECTATIONS FOR WOMEN AT THE TIME, SHE WAS DRAWN TO STUDY MEDICINE AND SOON DISCOVERED A PASSION FOR THE DEVELOPING NERVOUS SYSTEM.

HER DREAMS OF BEING A SCIENTIST WERE INTERRUPTED WHEN MUSSOLINI'S GOVERNMENT PASSED LAWS BARRING JEWS FROM PROFESSIONAL CAREERS.

NOT GIVING UP, RITA SET UP A LABORATORY IN HER BEDROOM.

SHE HAD TO BUILD IT TWICE, AS HER FAMILY FLED THE DESTRUCTION OF WORLD WAR II.

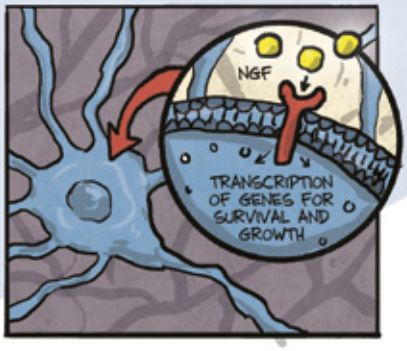
INSPIRED BY THE WORK OF VIKTOR HAMBURGER, RITA BEGAN STUDYING HOW NERVES DEVELOPED IN CHICK EMBRYOS.



SHE CONFIRMED THAT CERTAIN TISSUES PRODUCE A CHEMICAL THAT ENCOURAGES THE GROWTH AND PROPAGATION OF NERVE CELLS.

AT THE HEIGHT OF THE WAR, RITA SERVED AS A DOCTOR FOR REFUGEES IN FLORENCE.

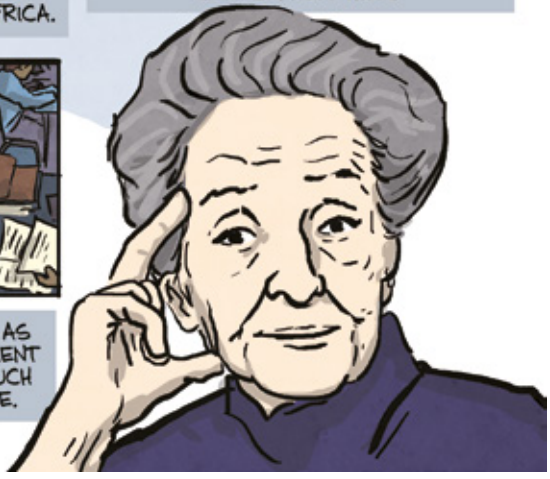
WHEN THE WAR ENDED, SHE WAS INVITED TO THE U.S., WHERE SHE CO-DISCOVERED NERVE GROWTH FACTOR (NGF), A KEY CHEMICAL IN NEURAL DEVELOPMENT. SHE WAS AWARDED THE NOBEL PRIZE 30 YEARS AGO IN 1986.



IN LATER YEARS, RITA FOUGHT FOR GOVERNMENT FUNDING OF SCIENCE AND STARTED A FOUNDATION TO INCREASE LITERACY FOR GIRLS IN AFRICA.

NGF IS NOW BEING USED AS AN EXPERIMENTAL TREATMENT FOR BRAIN DISORDERS SUCH AS ALZHEIMER'S DISEASE.

RITA DIED IN 2012 AT THE AGE OF 103. DESPITE ALL THE CHALLENGES, SHE MAINTAINED: "ABOVE ALL, DON'T FEAR DIFFICULT MOMENTS. THE BEST COMES FROM THEM."



Dwayne Godwin is a neuroscientist at the Wake Forest School of Medicine.
Jorge Cham draws the comic strip *Piled Higher and Deeper* at www.phdcomics.com

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