POLICE VIOLENCE: WHY COPS LOSE CONTROL *page 44*

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AUTISM GENES: Cracking the Code
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How reimagining the past shapes our memories, emotions and future

What If...

Sonic Surgery

Older and Happier: The Positivity Effect

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A World of What-ifs

As children, we inhabit a land of imagination. Our bedroom is a forest, a snowbank is a fortress, and we are elves, warriors, princesses and superheroes. Most of us put away fantasy in adulthood but with an important exception (and I don't mean Comic-Con). As Felipe De Brigard of Duke University's Center for Cognitive Neuroscience explains in our cover story, "Why We Imagine," beginning on page 28, we routinely unleash our imagination in reveries of how things might have gone differently. "We dip into alternative realities with a frequency and ease," De Brigard writes, "that suggest this habit is core to the human experience."

Why we engage in what cognitive scientists call "counterfactual" thinking is the question our article explores, drawing on research about the distinct logic of such musings and the impact on memory, emotion and motivation. In conjunction with the story, we asked visitors to our Web site to share their own what-ifs, which you can find at www.ScientificAmerican.com/WhatIfMoments.

In cities around the U.S., from Cleveland, to Ferguson, Mo., to Houston, communities have been pondering some more troubling counterfactuals: What if 12-year-old Tamir Rice had been playing with a ball instead of a toy gun in a Cleveland park last November? What if Sandra Bland had used a signal when she changed lanes while driving in Waller County, Texas, in July? More critically, what would have happened if the law-enforcement officers who confronted Rice and Bland had kept their cool? Surely these young people would be alive today. In a timely story, Rachel Nuwer reviews the factors that contribute to police violence and what we can do about it. "When Cops Lose Control" begins on page 44.

Parents of youngsters who have autism often torture themselves with what-ifs, wondering if there was something they could have done differently to prevent the disorder. Simon Makin's article, "What Really Causes Autism," starting on page 56, may offer some relief. In it, Makin sorts through the explosion of recent research showing that autism is primarily a genetic disease and discusses how these findings are beginning to open the door to new therapies.

Here's one more what-if. What if growing older made you happier, not just grumpier and creakier? Hmm. What if you turned to page 64 to find out more?

Claudia Wallis
Managing Editor
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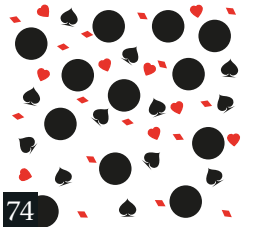
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LEARNING TO WALK AGAIN

I was amazed at the article by Amanda Boxtel, "Walking 2.0," and at her undaunted courage in her efforts to walk after being paralyzed in a skiing accident. Her story of learning to use an exoskeleton is truly remarkable and a great example for everyone faced with disabilities.

I was particularly interested in Boxtel's story because I suffer from some wearing out of lower back vertebrae. My ailment is commonplace in the aging population, and the only solution seems to be tailored exercises and painkillers. Given that medical technology today can circumvent some of the spinal problems with this impressive exoskeleton support, I believe that within the next 100 years technology will be able to replace worn-out or broken spinal disks.

Charles G. Roy
via e-mail

Although the article about the exoskeleton was very interesting, I would like to point out that there are other options for exoskeletons that may be more suitable for other people. For example, Rex Bionics has one that does not require the use of crutches and can be used at home without a physical therapist being present. In fact, there are at least two or three other exoskeletons that were not mentioned in the article.

Michael Landau
via e-mail

THE EDITORS REPLY: *Landau is correct that there are more manufacturers and devices available than we could detail. We focused on devices that are available in the U.S. and approved by the FDA. Currently the Rex Bionics exoskeleton for home use is not available in the U.S. We hope that when we return to this topic in the future, we will have an opportunity to take a more global look at the subject.*

FIXING VIDEO GAME RESEARCH

The tired mantra at the conclusion of thousands of psychological studies that "more research is needed" certainly applies to research on the effects of violent video games, as stated in "How Violent Video Games *Really* Affect Kids," by Greg Toppo. More important, the mantra should also read that "better research is needed." Most research on this topic uses correlational designs, small samples, laboratory conditions, and self-report indices of aggression or violence proneness. Such weak causal inference research has not been very helpful in getting the answers the public needs. These studies have also focused on what I call "small v" violence, indexed in those self-report questionnaire measures of violence and aggression that are usually poorly validated, or not validated at all, against real-world actual violence—that is, "big V" violence.

As a psychological researcher myself, I think job number one is to conduct this research out there where the actual violence is, where the pain is and where the possibilities of remediation are strong. It will be a challenge to our ingenuity to conduct violent video game research beyond the monastery walls, but it is essential that it be done, and replicated, and replicated.

Frank Farley
Temple University

EARLY-LIFE TRAUMA

The first sentences of the article "Before the Trauma," by Moises Velasquez-Manoff, grabbed my attention with a flashback of my own. Like an explosive device concealed diabolically underneath a tray of cookies, when I was eight, my 12-year-old brother hid a rubber cockroach between two slices of roast beef at our Sunday dinner, which until

then had been my favorite meal. There were many other abuses at my brother's hands that my parents did nothing to prevent. Velasquez-Manoff writes, "A consistent finding is that early-life adversity increases the risk of PTSD many years later." This is a true statement. I suffered PTSD as a young bride of 22 after being raped by a trusted boss. My early experiences taught me I was not valued; these experiences were followed by others. I've never been in the military, but I've fought my own wars. Thanks for this challenging article. I'm sure many others in recovery will benefit from the research.

Kathryne B.
via e-mail

WHAT IS INTELLIGENCE?

The presumably intentional hyperbole in the final sentences of Christof Koch's "Intelligence without Sentience" [Consciousness Redux] notwithstanding, the only trouble with his article is the failure to define "intelligence." The implied definition seems to be along the lines of "able to be made to carry out a defined task (in some cases through a 'learning' mechanism)." Yet by that definition, very many things count as intelligent—yet appear to lack what we're really after. The laser sensor at the supermarket is very good at opening the door for me just as I approach, and as Daniel Dennett once pointed out, a home thermostat quite intelligently monitors the heat in my home and operates the furnace to keep me comfortable. Deep Blue, Watson and DeepMind are all examples, I think, of what John Searle has famously called "weak AI": a simulacrum of intelligence, not the genuine article.

True intelligence requires meaning. The system must *know*, must *understand*, what it is doing to count as being truly intelligent. I do not know if consciousness is a necessary part of this equation, but I do believe it harms AI research itself to label systems such as DeepMind as intelligent. To do so sets the bar too low. True artificial intelligence, whether it possesses the ever elusive consciousness or not, will, at the very least, *know* what it is doing. Before we declare that there can be intelligence without consciousness, we need to make sure we've found real intelligence to begin with.

Benjamin J. Stenberg
Oregon State University

KOCH REPLIES: *I fully agree with you on the crucial difference between weak and strong AI, as I spelled out in my essay in the September/October issue of* Scientific American Mind. *The extent to which strong intelligence, whether of the human or of the computer variety—and defined as the ability to achieve a variety of goals within a range of natural and artificial environments—requires either "meaning" or consciousness is an open question. Unlike many other questions in philosophy, however, we may know the answer before the century is out.*

TAMPING DOWN TICS

I found "Adapt and Overcome," by Michael T. Ullman and Mariel Y. Pullman [Perspectives], very interesting. In 1990 my then four-year-old daughter was diagnosed with Tourette's and attention-deficit/hyperactivity disorder. Her school years were traumatic, with teasing and bullying. In an attempt to alleviate the situation, she and I tried to identify what other body movement, something that would be less visible, could provide the necessary relief from the tic impulse. Another way of scratching the itch!

For instance, when she had a facial tic, she tried to move the reaction to the impulse down her neck to her chest or diaphragm to internalize it. When she had a vocal tic, she turned it into snippets of song humming. As the tics waned and returned, she discovered that they would always start in the original site again. Her ability to move the tic would then kick in. She still uses this method whenever tics arise. Today she is a well-adjusted, socially confident 30-year-old.

An interesting aside: when I told her neurologist and general practitioner what she was doing, they told me not to encourage it because it was too stressful and cruel!

Judy S.
via e-mail

ERRATA

"Before the Trauma" incorrectly stated that the insula and dorsal anterior cingulate cortex are part of the prefrontal cortex. These are three distinct brain areas, all of which are affected by early childhood maltreatment.

"Out of Sync," by Emily Laber-Warren [September/October 2015], misstated Brant Hasler's specialty. He is a psychologist.

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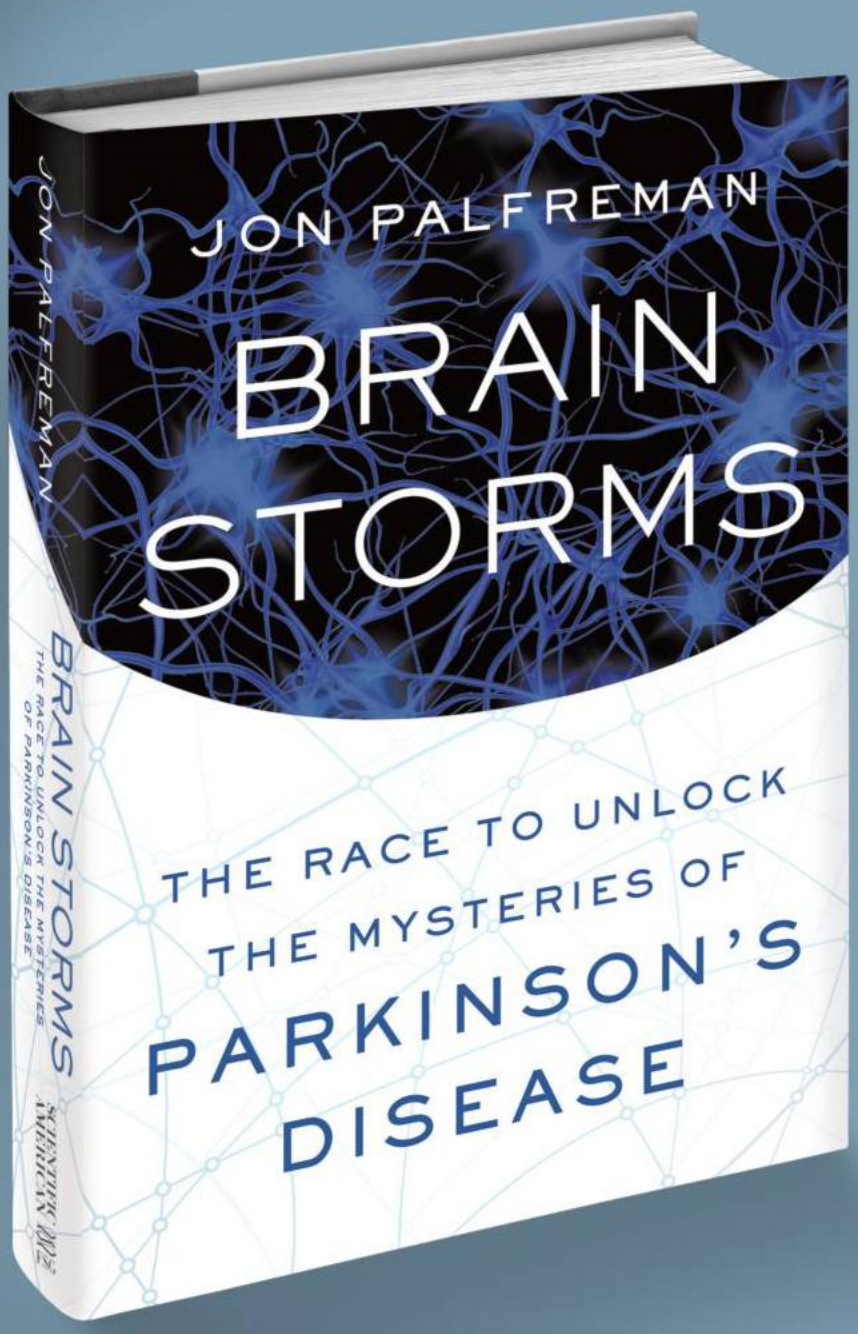
A Top Ten Science Book for Fall 2015, *Publishers Weekly*



"Award-winning journalist Palfreman's fast-paced, captivating, and crisp narrative of patients, doctors, and researchers is part scientific investigation, part medical detective story, and part memoir, and it **opens wide a window into the world of Parkinson's.**"
—*Publishers Weekly* (starred review)

"***Brain Storms*** **is a sweeping survey—and a fascinating discovery narrative**—of one of the great neurological scourges of our time. In this era of brain science, Jon Palfreman's book points to remarkable vistas of research that promise hope to millions." —SANDEEP JAUHAR, *New York Times*–bestselling author of *Doctored* and *Intern*

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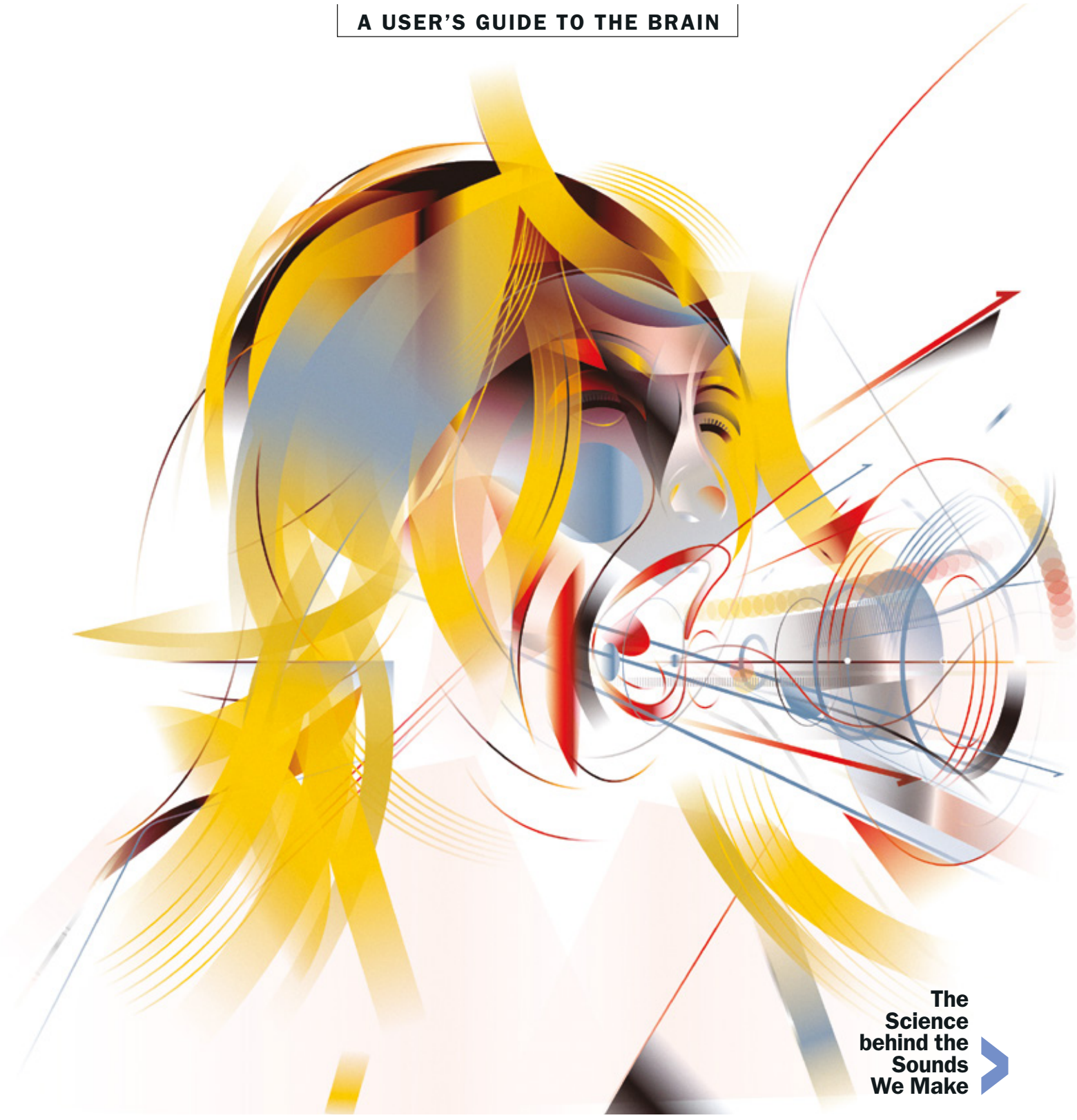
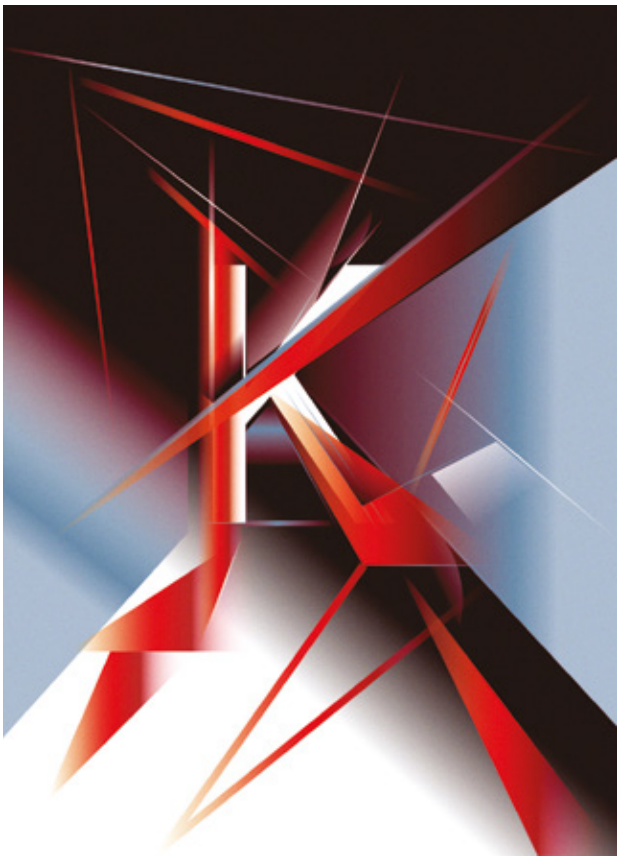


The Science behind the Sounds We Make

THE SOUNDS WE MAKE

The building blocks of language vary widely from culture to culture, from the clicks of the San people to the musical tones of the Chinese. Yet common roots can be found across most tongues. Recent studies offer intriguing clues about why we link certain consonants to certain types of objects, why screams are so piercing and how we hear rhymes.

ILLUSTRATIONS BY LEANDRO CASTELAO



The Universal Meaning of Consonants

People from all over the world associate certain letters with round or spiky shapes

They are just nonsense words, but for decades *bouba* and *kiki* have been studied by linguists, who are fascinated by the way they convey meaning across a broad spectrum of languages. Beginning as far back as the 1920s, study after study has demonstrated that children and adults, regardless of the languages they speak, match the words *bouba* and *malumi* with round shapes and *kiki* and *takete* with spiky shapes. Why this is so has remained a puzzle. In most words, consonants and vowels do not have any inherent link to meaning. The "o" in "octagon," for example, is not naturally connected to eight-sided shapes. So what could possibly be special about *bouba* and *kiki?*

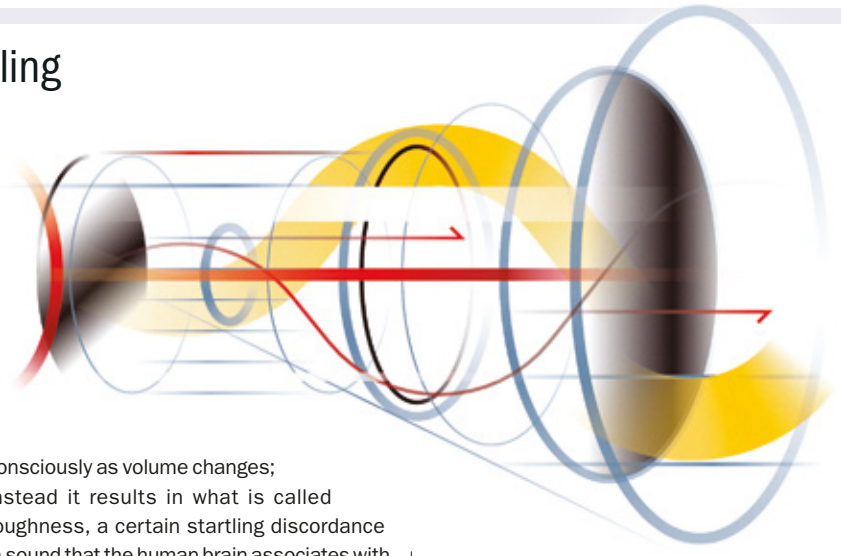
Scientists now have a partial answer: consonants seem to carry significance apart from the words they help to form. In a recent study of 71 French speakers published in the journal *Language and Speech,* researchers in Europe led by Mathilde Fort of the École Normale Supérieure in Paris showed that people consistently matched *b, m* and *l* words with round shapes and *k* and *t* words with spiky shapes, regardless of the vowels they are combined with. On the face of it, this result suggests that *bouba* and *kiki* may be similar to English onomatopoeic words such as "crash" and "crunch," where the consonants supply a sound-symbolic meaning of noisy impact, regardless of the vowels. The difference would be that *b, m* and *l* supply their meanings in many languages, not just in English, as do *k* and *t*.

A small follow-up experiment, however, showed that the effect was not limited to a few consonants. A sample of 23 people also matched *d, n, s, p, sh* and *zh* words with round shapes and *f, v* and *z* words with spiky shapes. As before, subjects seemed to ignore the vowels. This result, which sound symbolism cannot explain, suggests that we humans have fundamental reactions to certain sounds, which persist despite the vastly different soundscapes of the world's existing languages. The consonants in each group must have something in common that triggers such associations in our brain, but scientists have not figured out what that property is yet—simple acoustics cannot explain it. In any case, the finding shows that consonants in general have an outsize role to play in language.

Indeed, certain languages such as Arabic and Hebrew clearly prioritize consonants over vowels, often omitting vowels from texts. The root for "writing" in Arabic is */ktb/*. Fill that in with different vowels to get a variety of writing-related words, such as *kataba* ("he wrote"), *yaktubna* ("they write") and *kitab* ("book"). The presence of such languages in the world—and the absence of any languages that prioritize vowels—adds further support to the idea that consonants are key. Vowels remain necessary because they make it possible to say words out loud. But it is consonants that do the hard work of conveying meaning. —*Anne Pycha*

Why Screams Are So Startling

The acoustics are perfectly tailored to grab our attention



If there is one sound that bettered our ancestors' chances of survival, it might be the scream. When a baby needs food, it hollers; if a ravenous lion prowls a little too close, a blood-curdling shriek alerts the tribe. Yet from an acoustic standpoint, screams—and how our brain processes the sound—have been largely overlooked by researchers, until now. A study published in July in *Current Biology* found that screams are sonically unique in a way that perfectly captures our attention.

By analyzing screams culled from YouTube videos, films and volunteer shriekers, researchers led by neuroscientist David Poeppel, who runs a language-processing laboratory at New York University, found that screams occupy a dedicated position on the auditory spectrum. Specifically, what sets them apart from other human vocalizations is how fast they change in loudness. Normal speech has only slight variations in loudness—changing at a rate of just four to five times per second—whereas screams violently clamor through our vocal cords varying in volume 30 to 150 times per second. This rapid, large variation is too fast to be perceived consciously as volume changes; instead it results in what is called roughness, a certain startling discordance in sound that the human brain associates with fear. To this end, Poeppel and his colleagues used functional MRI to show that increases in roughness raise the activation of the amygdala, the brain's fear and emotion center.

Roughness is what allows screams to outcompete other sounds. Plenty of things are loud—jet engines, for example. Yet a wailing five-year-old tends to cut through the roar and grab our attention. The unique spectral qualities of screams are also thought to reduce the incidence of false alarms from other loud but nonrough sounds. Incidentally, it turns out engineers have—knowingly or not—been taking advantage of roughness for decades: as Poeppel's work shows, most sirens and alarms also oscillate in loudness in the same wide, chaotic frequency pattern as screams do.

Poeppel plans on exploring next whether or not infant screams have the same roughness patterns as adult ones. He also hopes to look for correlates in the animal world. "Screams are arguably the oldest vocalizations," he says, "so understanding more about their properties illuminates fundamental features of the mind and brain."

—Bret Stetka

Sounds associated with basic emotions—anger, fear, disgust, happiness, sadness and surprise—appear to be universally recognized across cultures.

How to Rhyme Like a Rapper

Hip-hop artists understand that our ears forgive mismatches

In his critically acclaimed song "Empire State of Mind," rapper Jay Z used conventional rhymes such as *made-Wade,* as well as partial rhymes such as *life-light.* Long considered part of the verbal artistry of hip-hop, this latter type of word play also reflects a sophisticated awareness of what consonants sound like in different parts of words. In a recent study examining the songs of seven individual rappers, researchers found that partial rhymes such as *life-light,* in which the last consonant differs, occurred very frequently. Previous laboratory work had already shown that different consonants at the end of a word often sound similar to people, and the new study suggests that rappers capitalize on this fact to create pairs of words that seem to rhyme, even when they do not. The study also showed that partial rhymes such as *follow-tomorrow,* where the middle consonant differs in *ollow* versus *orrow,* occurred in the songs only infrequently. Consonants in the middle of a word rarely sound similar to people, and rappers appear to recognize this tendency, using such pairs sparingly. The implication is that—not surprisingly—rappers possess a subtle but deep understanding of how people perceive speech. —*A.P.*

(PHARMA WATCH)

The Promise of Alzheimer's Drugs Revived

False starts but maybe not false hope for drugs that could slow the disease's progression

With millions of baby boomers fast approaching old age, Alzheimer's disease diagnoses are set to spike—and the hunt is on to find medications that can slow or halt the progression of this most common form of dementia. Many pharmaceutical companies pinned high hopes on monoclonal antibodies, drugs designed to latch onto a toxic protein that builds up in the brain of sufferers and triggers the immune system to break it down. In preliminary studies during the past decade, however, these drugs often failed to outperform placebos. Now several new analyses may have resurrected their original promise.

In July three research teams presented data at the Alzheimer's Association International Conference in Washington, D.C., suggesting that monoclonal antibodies could potentially stall Alzheimer's relentless progression—provided they could be given early enough and at high-enough doses. These experimental drugs all target beta-amyloid, a protein fragment at the heart of a widely accepted theory about how Alzheimer's destroys memory. Every cell in the body produces beta-amyloid, but if the brain cannot clear it fast enough, it starts to clump together, gumming up synapses and amassing into neuron-killing plaques. Antiamyloid monoclonal antibodies are designed to bind to the fragments and flag them for removal by the immune system.

At the meeting, pharmaceutical company Biogen presented new findings from an ongoing study of its monoclonal candidate, aducanumab. Biogen had announced with much fanfare in March that the drug significantly reduced beta-amyloid plaques seen on PET scans and slowed cognitive impairment in 166 patients with mild Alzheimer's. Patients on the top dose tested—10 milligrams per kilogram of body weight—maintained the highest memory scores but also experienced more localized brain swelling, a side effect linked to leaky blood vessels. So midtrial they introduced what they hoped would be a Goldilocks dose—not too much, not too little. But it was not just right. Biogen's researchers revealed that six milligrams produced even less benefit than three milligrams on one measure of cognitive function. The search for the perfect dose, and definitive proof of the drug's potency, will continue during an upcoming five-year study.

In the meantime, researchers at Eli Lilly described potentially encouraging results from an extension of a large failed trial of solanezumab. To highlight this monoclonal antibody's efficacy, they focused only on patients with early disease and used a so-called delayed-start analysis—the first ever for an Alzheimer's drug. At the start of the 3.5-year trial, they randomly assigned 1,322 patients to either placebo or active treatment. After 80 weeks, everyone in the placebo group began taking solanezumab as well.

Both groups continued to show worsening symptoms, but treatment seemed to slow the pace by about one third. Of significance, the placebo

GETTY IMAGES (*woman*), FOR ILLUSTRATION PURPOSES ONLY; © ISTOCK.COM (*pills*)

group never caught up to the cognitive scores of patients who received solanezumab from the start. The researchers interpret this finding as tantalizing evidence that the drug is mopping up beta-amyloid in the brain and tempering its toxicity. If it were simply treating symptoms, the delayed-start control group should have made the same gains as the first group—just later on. A confirmation study is under way.

And scientists at Hoffmann–La Roche have described new findings about yet another antiamyloid drug, gantenerumab. A large trial of this monoclonal antibody was canceled in December 2014, when it failed to show any measurable effects. Yet when the researchers reanalyzed the data, considering only patients with very early and rapidly progressing disease, they found that gantenerumab had reduced beta-amyloid on PET scans for that group. It also reduced levels of tau—another protein that builds up inside neurons as Alzheimer's advances, forming tangles that fritz normal cell function.

All three reports underscore the importance of early intervention. At a certain point, it may be too late to stem the amyloid tide. Several other trials are now probing whether antiamyloid drugs might be even more powerful when used preventively. The so-called A4 study, a joint effort of the National Institutes of Health, Eli Lilly and several nonprofit organizations, is testing solanezumab in patients who do not yet display memory deficits but have increased levels of beta-amyloid on PET scans. Two more investigations are exploring solanezumab's effect on healthy people who carry genetic mutations that put them at high risk for inheriting Alzheimer's.

For all the rekindled hope around monoclonal antibodies, other classes of drugs in earlier stages of testing may wind up doing as much or more to help Alzheimer's patients. "Some of the most advanced stages of development are in drugs targeting beta-amyloid," says Heather Snyder, director of medical and scientific operations at the Alzheimer's Association, "but there are other clinical trials targeting insulin, tau, inflammation, and mechanisms behind neuron growth and health. We will need to identify all the biological changes taking place and intervene with all the treatments we have available—both medications and lifestyle changes—if we are going to reduce the risk or stop or slow the progression of Alzheimer's." *—Kristin Ozelli*

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How the Brain Purges Bad Memories

A brain circuit has been isolated that allows us to forget fear, suggesting a treatment target for anxiety disorders

The brain is very good at alerting us to threats—and it is also adept at letting us know when a threat no longer exists. Sometimes this system fails, however, and unpleasant associations stick around—a malfunction thought to be at the root of post-traumatic stress disorder (PTSD). New research has identified a neuronal circuit responsible for the brain's ability to purge bad memories, findings that could have implications for treating a broad range of anxiety disorders, including PTSD.

Previous work has consistently implicated two areas of the brain as contributing to and regulating fear responses. The amygdala is involved in emotional reactions, and it flares with activity when we are scared. The prefrontal cortex steps in to calm us down when a particular threat turns out to be harmless. A large body of work implicates the two areas in fear memory, but because of their connections to many other parts of the brain, it was unknown whether their joint effort was truly at the root of overcoming fear. The new study, led by Andrew Holmes of the National Institute on Alcohol Abuse and Alcoholism, confirms that a working connection between the two brain regions is necessary to do away with fearful associations.

The researchers worked with mice trained to fear a sound paired with a foot shock. Typically if such mice are later exposed to the repeated sound without a foot shock, they will learn that the noise is harmless and will stop being afraid. In the new study, the researchers disrupted the mice's amygdala–prefrontal cortex connection using optogenetics, which controls specific neurons with fiber-optic lights. The authors found that disrupting this key connection prevented the mice from overcoming the negative association with the benign tone—they continued to fear the sound long after the foot shocks disappeared. They also discovered that the opposite was true: stimulating the circuit resulted in faster extinction of fearful memories.

As Holmes explains, the amygdala and prefrontal cortex are two major hubs in a complex communications network. In the case of impaired fear extinction such as PTSD, however, it appears that just the one connection between the two regions is faulty, not the hubs themselves. As such, the efforts of previous experiments to treat PTSD by altering activity in one of these major brain areas have probably been overkill.

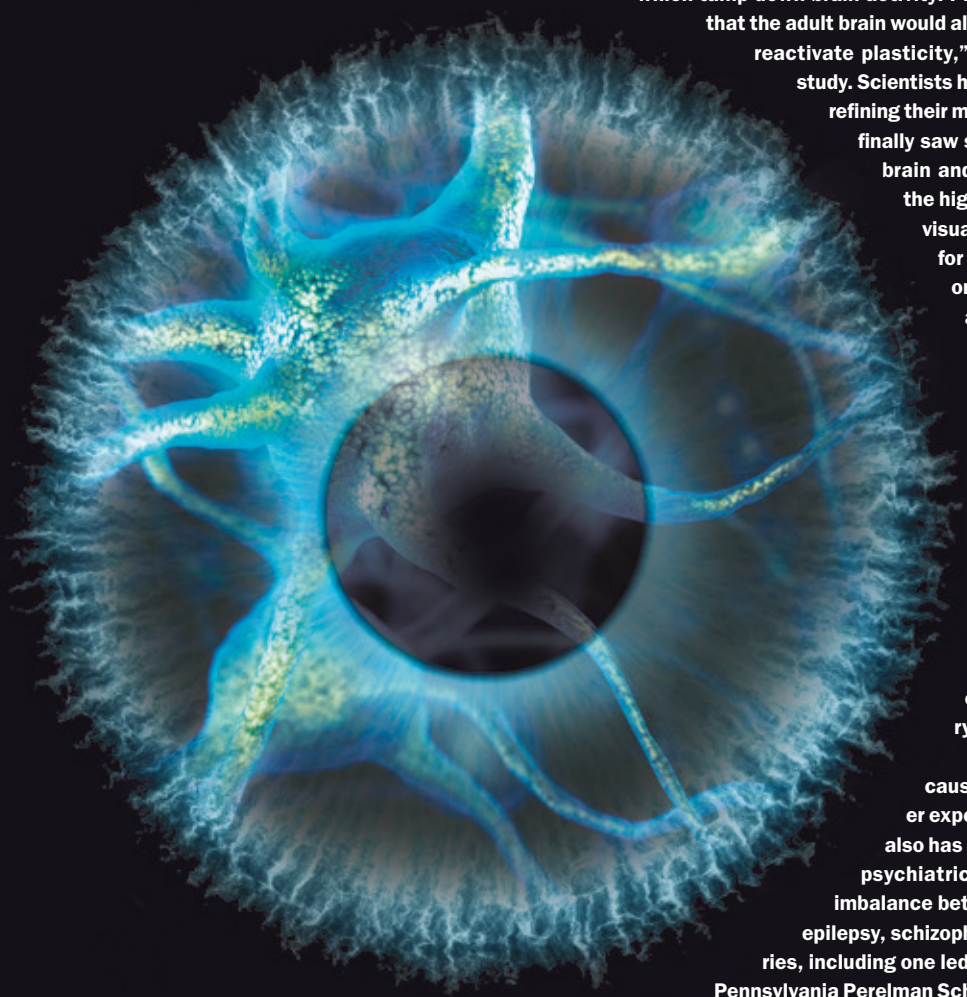
The new finding suggests that researchers should explore medications that act on this specific fear circuit. Holmes believes that healthy fear extinction relies on "neural plasticity," the brain's ability to make new neuronal connections, which is in part influenced by the brain's native cannabinoids, compounds that regulate neurotransmitters. Drugs that alter the cannabinoid system, such as THC, the active component in marijuana, could temporarily make the fear circuit more plastic—perhaps allowing clinical techniques, such as exposure therapy, to better alleviate anxiety. *—Bret Stetka*

FUTURE FOCUS

NEURON TRANSPLANTS MAY ONE DAY RESTORE VISION

Young brains are plastic, meaning their circuitry can be easily rewired to promote learning. By adulthood, however, the brain has lost much of its plasticity and can no longer readily recover lost function after, say, a stroke. Now scientists have successfully restored full youthful plasticity in adult mice by transplanting young neurons into their brain—curing their severe visual impairments in the process.

In a groundbreaking study published in May in *Neuron*, a team of neuroscientists led by Sunil Gandhi of the University of California, Irvine, transplanted embryonic mouse stem cells into the brains of other mice. The cells were primed to become inhibitory neurons, which tamp down brain activity. Prior to this study, "it was widely doubted that the adult brain would allow these cells to disperse, integrate and reactivate plasticity," says Melissa Davis, first author of the study. Scientists have been attempting such a feat for years, refining their methods along the way, and the Irvine team finally saw success: the cells were integrated in the brain and caused large-scale rewiring, restoring the high-level plasticity of early development. In visually impaired mice, the transplant allowed for the restoration of normal vision, as demonstrated by tests of visual nerve signals and a swimming maze test.



The scientists have not yet tested the transplanting technique for other neurological disorders, but they believe the technique has potential for many conditions and injuries depending on how, exactly, the new neurons restore plasticity. It is not yet known whether the proliferation of the transplanted cells accounts for the restored plasticity or if the new cells trigger plasticity in existing neurons. If the latter, the treatment could spur the rewiring and healing of the brain following traumatic brain injury or stroke.

The team used inhibitory neurons because they showed the most promise in earlier experiments. But that specific type of neuron also has particular clinical promise because many psychiatric and neurological disorders involve an imbalance between excitation and inhibition, including epilepsy, schizophrenia and chronic pain. Several laboratories, including one led by Stewart Anderson of the University of Pennsylvania Perelman School of Medicine, have demonstrated that transplanting inhibitory neurons from healthy mice has improved symptoms in mice with models of those diseases. The new method would allow for more widespread brain changes, potentially eradicating the disease entirely. For people who have not been helped by medications, "a heroic treatment such as neuron transplantation could be potentially life changing," Anderson says.

Many obstacles remain before neuron transplantation happens in humans. First, mouse stem cells may not be effective or safe for transplantation into humans, and scientists do not yet know how to coax human stem cells into becoming the type of precursor neurons needed for the procedure. In addition, transplanted cells take more than a month to mature in the recipient mouse brain; human cells would in theory take considerably longer, perhaps years.

Despite these hurdles, experts are excited about the breakthrough. They believe neuron transplantation may someday provide a cell-based therapy to effectively and, more important, permanently treat age-related and developmental diseases.

—Jessica Schmerler

OLEKSIY MAKSYMENKO *Corbis (neuron)*; © ISTOCK.COM (*pupil*)

How Do You Solve a Problem Like an Earworm?

Chewing gum and distracting yourself might get rid of that song stuck in your head—or you might just have to learn to like it

If you are one of the 92 percent of the population who regularly experience earworms—snippets of music that pop uninvited into your head and won't go away—you might wish there was a way to make them stop. Earworms are a generally benign form of rumination, the repetitive, intrusive thoughts associated with anxiety and depression.

Psychologists have long been looking for ways to turn off those unwelcome thoughts, and now a study from the University of Reading in England suggests a fresh approach: chew some gum. Psychologist Philip Beaman and his colleagues found that college students exposed to a catchy song snippet who then chewed gum reported fewer earworms than those who did not chew. The act of chewing gum, as with silently reading, talking or singing to yourself, engages the tongue, teeth and other parts of the anatomy used to produce speech, called subvocal articulators. These subvocalizations lessen the brain's ability to form verbal or musical memories.

For some people, gum chewing might just be enough to head off continuous replays of "Maria" from *The Sound of Music*. The technique probably will not do much for deeply entrenched earworms, however. I personally have had the same one stuck in my head for more than 30 years, a series of nine notes from a tune I have never been able to name. (Experts say that such persistent earworms are very rare but not entirely unheard of.) Chewing gum did not help.

Other strategies for eradicating earworms include what British music psychologist Victoria Williamson of the University of Sheffield describes as "distract and engage." The most effective distractions, she explains, are verbal or musical: chanting a mantra, reciting a poem, listening to a different song, even playing an instrument. They work by activating the component of working memory involved in earworms, a storage and rehearsal cycle called the phonological loop. "If you fill it up with something else that occupies the same circuitry, there's not enough left to make the earworm," Williamson says.

Focusing on a specific mental task—say, thinking through your schedule for the week—can also rout a repetitive melody. Yet if the task is either too easy or too hard, your mind tends to fall back on the earworm. It has to take up just the right amount of cognitive load—what Ira Hyman, a professor of psychology at Western Washington University, calls the Goldilocks effect. Researchers at the University of Cambridge designed what they believed was the perfect exercise: mentally generating random numbers, at about one a second, without ever repeating a number.

The other common approach is to engage the earworm. Instead of trying not to think about it, you deliberately listen to the entire song, start to finish, several times in a row. Most earworms are fragments, which very likely contributes to their stubborn longevity; incomplete memories last longer than complete ones, a phenomenon known as the Zeigarnik effect. By completing the fragment, Williamson says, you might drive the song from your conscious memory.

Or you might not. Neither distraction nor engagement worked for me. In the long run, some experts say, the best strategy might simply be learning to enjoy the concerts in your head. I've been trying to identify, disrupt and interrupt my earworm for three decades, with no luck. Occasionally it subsides for a day or two, and I think it's gone; then I find myself silently humming those same nine notes. I have come to think of it as the sound track for my life. And it could be worse. I could find myself silently breaking into "It's Friday, Friday, gotta get down on Friday."

—Harriet Brown

Sizing Up Earworms

- 15 to 30 seconds: the estimated length of a typical earworm episode
- 92 percent of people experience an earworm at least once a week
- 99 percent of the population experiences earworms occasionally
- Most people describe earworm episodes as benign, but:
  15 percent find their earworm "disturbing"
  33 percent describe their earworm as "unpleasant"

JUAN SILVA *Getty Images*

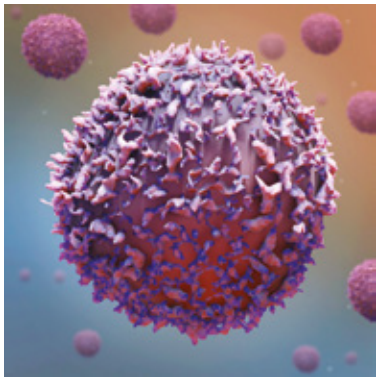
BREAKTHROUGH

MISSING LINK FOUND BETWEEN THE BRAIN AND IMMUNE SYSTEM

The discovery may help explain some long-standing mysteries about neurological disease

Textbooks have traditionally taught that when it comes to the immune system, the brain and body are separate entities. When exposed to foreign objects such as bacteria or transplant tissue, the body stirs up a torrent of immune activity: white blood cells devour invading pathogens and burst compromised cells; antibodies tag outsiders for destruction. Except, that is, in the brain, where the blood-brain barrier bars both foreign bodies and immune cells from entry. New research, however, uncovered a previously unknown line of communication between our brain and immune system. The report in July in *Nature* (*Scientific American Mind* is part of Springer Nature) adds to a fast-growing body of research linking the brain and bodily defenses.

As early as 1921, scientists recognized that the brain is different, immunologically speaking. Tissue grafted into the central nervous system sparks a far less hostile response than tissue grafted to other parts of the body, prompting scientists to consider the brain "immunologically privileged." Experts have long pointed to the brain's apparent lack of lymphatic drainage as one reason for this privilege. The lymphatic system is our body's third set of vessels, along with arteries and veins. Lymph nodes—stationed periodically along the vessel network—serve as storehouses for immune cells. In most parts of the body, foreign invaders trigger the release of these cells through the vessels into the bloodstream.



The new study discovered that the brain is connected to the lymphatic system after all. Working primarily with mice, senior author and University of Virginia neuroscience professor Jonathan Kipnis and his group identified a hitherto undetected network of lymphatic vessels in the meninges—the membranes that surround the brain and spinal cord—that shuttle fluid and immune cells from the cerebrospinal fluid to the deep cervical lymph nodes in the neck. Kipnis and his colleagues had previously shown that a type of white blood cell called a T cell (*shown above*) in the meninges is associated with significant influence on cognition and hence were curious about the role of meningeal immunity on brain function. Using neuroimaging on mouse meninges, the team noticed that T cells were present in vessels separate from arteries and veins.

The newly discovered vessels, which were also identified in human samples, could explain the long-standing conundrum of how the immune system manages to contribute to neurological and psychiatric disease. For example, some cases of multiple sclerosis are thought to result from autoimmune activity in response to an infection in the central nervous system and cerebrospinal fluid. "It's early to speculate," Kipnis says, "but I think that alteration in these vessels may affect disease progression in those neurological disorders with a prominent immune component, such as multiple sclerosis, autism and Alzheimer's disease."

Some mental illnesses, including depression and schizophrenia, have also been linked with abnormal immune activity and inflammation. Yet scientists have not been able to uncover the underlying mechanism. The new finding suggests a tantalizing target for research and, perhaps one day, drugs. Josep Dalmau, a neurology professor at the University of Pennsylvania who was not involved with the study, agrees that the findings could help explain the initiation, maintenance and perhaps worsening of autoimmune disorders that affect the brain.

In light of the news, the textbooks might need some revising. "It has become increasingly clear that the central nervous system is *immune-different* rather than *immune-privileged,*" he says. *—Bret Stetka*

New Experiences Boost Old Memories

Recall can improve for events that seem mundane but later prove to be important

What makes for a long-lasting memory? Research has shown that emotional or important events take root deeply, whereas neutral or mundane happenings create weak impressions that easily fade. But what about an experience that initially seemed forgettable but was later shown to be important? Animal research suggested that these types of older memories could be strengthened, but scientists had not been able to replicate this finding in humans—until now. New evidence suggests that our initially weak memories are maintained by the brain for a period, during which they can be enhanced.

In the recent study published in *Nature,* psychologists at New York University showed 119 participants a series of images of tools and animals. A few minutes later the subjects saw a new set of images, with an electric shock paired with either the tools or the animals, to increase the salience of just one of those categories. The participants' memories for both sets of images were then tested either immediately, six hours later or the next day. Participants remembered images from the first neutral series better if they belonged to the same category (tool or animal) that was later paired with the shock.

The findings suggest that even if an event does not seem meaningful when it occurs, a later cue that the experience was important can enhance the old memory. Although research has not yet demonstrated this effect outside the laboratory, the scientists speculate it happens often in daily life. For example, imagine you meet several new people at a networking event. During a job interview days later, you discover that one of those acquaintances is on the hiring committee, and suddenly the details of your conversation at the networking event become vivid and memorable—whereas the conversations you had with others at the event fade with time.

Many questions remain, including how long after a memory is born it is susceptible to strengthening and what types of feedback will trigger the changes. First author Joseph Dunsmoor, a research psychologist at N.Y.U., expects that positive or rewarding outcomes, rather than shocks, will also do the trick. *—Emilie Reas*

TIM VERNON *Getty Images*

A GUIDE TO MASTERING YOUR WORLD

How to Be a Better *gift giver*

One of the best gifts I ever received was from my long-distance friend Kelly. When my second daughter arrived and life was thrown into that special brand of chaos that only parents with a toddler plus a newborn can know, a huge box arrived at the door. It wasn't a care package of cashmere onesies or a hand-knitted baby blanket. It was a Styrofoam cooler brimming with everything we needed for three or four meals' worth of Portillo's Chicago-style hot dogs: the tomatoes, the onions, the dill pickles, even the celery salt and the soft, seeded buns. For a ravenous breastfeeding mom and her sleep-deprived, Chicago-native husband, there was nothing we could have wanted more.

After looking into the research around gifting (and there's plenty of it), the reasons that cooler was such a home run are clear. Want to become that good a giver? Follow these three evidence-based rules for giving good presents—just in time for the holidays!

#1 Simple and practical is good. A 2009 study in the *Journal of Experimental Social Psychology* found that although givers tend to think a fancier, expensive gift will be appreciated more, receivers are actually happier with cheaper, more practical presents. In the experiment, friends gave one another a new pen (the pairs were students, for whom pens are always at a premium). The givers thought their friends would prefer a heavy, fancy, special-occasion pen, but the getters in fact preferred the cheaper, lighter, portable one. "You think that things like price and the effort you put into a gift will matter, but the person you're giving it to doesn't see the work that went into it or the price tag—they just have the actual thing to focus on and how it will fit into their life," says Nathan Novemsky, a professor of marketing at Yale University who has done quite a bit of research on gift giving himself.

In one of Novemsky's recent studies, participants filled out a survey in which they imagined either giving or getting a gift certificate to a restaurant. Givers thought people would like a voucher for a five-star place a few towns over—but receivers preferred gift cards for a restaurant that was middle of the road but right around the corner. Both men and women tended to prefer the practical choice.

#2 Don't overdo the gift wrap. When Novemsky told me about some research he is doing now that suggests wrapping a present in a plain brown paper bag—or not at all—might be better than something gorgeous and beribboned, I thought, "No way! This is total holiday heresy." (I spend a couple of hours in Target every December carefully choosing my new palette of Christmas wrapping paper and ribbons.) But it made sense once he explained: pretty wrapping raises expectations for a gift and increases the risk of the receiver being disappointed if the present doesn't live up to them. "It's like giving someone a Sears gift card in a Tiffany box," he says. So unless you're sure the gift is going to kill—there's a Tiffany ring in that Tiffany box—consider toning down the packaging.

#3 Ask what the person wants. I used to think my husband's family was super weird for giving one another gift lists at Christmas and on birthdays. Where's the surprise? The effort? The proof that you know the person so well that you can divine exactly what he or she wants without asking? But there comes a point in your life when you just don't want any more useless—though well-intentioned—junk. So when John asked me what I might like for my birthday last year, I told him exactly what I wanted: a new Roku—a sleek, little box to stream Hulu, Netflix and Amazon Prime onto our television. He looked at me with crazy eyes. "Electronics? Isn't that kind of ... not romantic or heartfelt or something?" I shrugged, "I dunno, maybe"—but I wanted it. When he gave it to me as requested, I was beyond thrilled. Research from Harvard and Stanford business schools published in 2011 found that gift receivers in general are much happier when they're given exactly what they asked for rather than something "thoughtful" that wasn't on their list.

This year, instead of filling John's stocking with random stuff I think he'll like, I'm going to ask him to cc me on his Christmas gift e-mail to his mom. And then I'll get him exactly what he wants. —*Sunny Sea Gold*

MÁGOZ (*gift giving*); PAUL PANTAZESCU © iStock.com (*globe icon*)

The Schizophrenia Spectrum

As with autism or depression, psychosis may not be an all-or-nothing condition

Most people have felt depressed or anxious, even if those feelings have never become debilitating. And how many times have you heard someone say, "I'm a little OCD"? Clearly, people intuitively think that most mental illnesses have a spectrum, ranging from mild to severe. Yet most people do not know what it feels like to hallucinate—to see or hear things that are not really there—or to have delusions, persistent notions that do not match reality. You're psychotic, or you're not, according to conventional wisdom.

Evidence is growing, however, that there may be no clear dividing line. Psychiatrists have long debated whether psychosis exists on a spectrum, and researchers have been investigating the question for more than a decade now. A 2013 meta-analysis, combining much of the existing data, by Jim van Os of Maastricht University in the Netherlands and Richard Linscott of the University of Otago in New Zealand, found the prevalence of hallucinations and delusions in the general population was 7.2 percent—much higher than the 0.4 percent prevalence of schizophrenia diagnoses found in recent studies. Now the most comprehensive epidemiological study of psychotic experiences to date, published in July in *JAMA Psychiatry*, has given researchers the most detailed picture yet of how many people have these experiences and how frequently. The results strongly imply a spectrum—and suggest that the standard treatment for a psychotic episode might be due for an overhaul.

The researchers, led by John McGrath of the University of Queensland in Australia, analyzed data from the World Health Organization's World Mental Health Surveys, a set of community surveys carried out between 2001 and 2009, involving 31,261 adults in 18 countries. After ruling out experiences caused by drugs or sleep, the researchers determined that 5.8 percent of the respondents had psychotic experiences. Two thirds of these people had had only one type of episode, with hallucinations being four times more common than delusions.

The psychotic experiences were typically rare, with 32 percent of sufferers having only a single episode and another 32 percent having two to five. The other third reported between six and more than 100. Having more than one type of experience was linked to having more in total. These people were not seeking help, and none had been diagnosed with a psychotic disorder. "Most people have only fleeting, sporadic experiences, but there's a subgroup that have a lot, and they're persistent," McGrath says.

The results suggest psychosis indeed exists on a spectrum, but whether it is distributed in a continuous way across

GETTY IMAGES

Benign Hallucinations?

Jenny does not have schizophrenia, but she has hallucinations. "I could feel Mark in the room, standing behind me," she says of one such experience. "My first love, whom I hadn't seen since I was a teenager, still guiding me, as he had ever since my hallucinations started taking definite shape. I glimpsed him out of the corner of my eye, stroking my spreading wings, reassuring me I'd made the right decision, to leave my old life behind and travel to England to be a journalist." Jenny, who requested that her real name be withheld for privacy, agreed to talk with me about her hallucinations, which she regards as benign. When she hallucinates, she always sees Mark, and he always offers her advice. He is the part of herself she turns to for guidance.

Jenny believes that her childhood experiences and her mother's mental health issues predisposed her to psychosis—perhaps not surprisingly, because there is a known genetic component. A study last year strongly implicated 108 genetic regions as culprits in schizophrenia. Psychologists have told Jenny that the content of her experiences may be related to a lack of adequate psychological support in childhood, causing her to internalize her own support network. Where mental health is concerned, it seems, nature and nurture are almost always inextricably intertwined. —*S.M.*

the population remains to be seen. "Is it that we all have a bit of schizophrenia in us, or are there some people who do, and some who don't?" Linscott asks. One complication is that what counts as a hallucination can be a difficult line to draw, and even carefully crafted research surveys can be open to interpretation. "It could be that what we see at the margins are these subtleties due to the language used in the questions," he says.

The psychotic experiences were slightly more common in women (6.6 percent) than men (5 percent), even though full-fledged schizophrenia is more prevalent in males. In addition, psychotic experiences were more prevalent among people living in middle- and high-income countries (7.2 and 6.8 percent, respectively) than low-income countries (3.2 percent). Being unemployed or unmarried or being from a relatively low-income family was also associated with higher rates of hallucinations and delusions. Socioeconomic and environmental factors such as stress are known risk factors for schizophrenia.

Psychotic experiences are sometimes markers of general psychological distress, McGrath explains: "They pop up in depression, anxiety disorders, a whole range of things." They also occur in healthy people [*see box on opposite page*], and ultimately the goal is to discover what determines why some people get a mild dose and are not distressed, whereas others go on to have serious illness. Answering this question could have important ramifications for helping those in distress. Treatment would look very different for a person whose psychotic experiences were linked to depression or anxiety disorders or were the one-time result of acute stress, compared with a person who is showing the first signs of schizophrenia.

The fact that psychosis may exist on a spectrum could also help ease the stigma attached to a schizophrenia diagnosis. That would be a huge boon to people who experience symptoms, no matter how mild or severe. —*Simon Makin*

Sex: Seniors Find Answers Online

Talking about the topic feels taboo to many older adults and their health care providers

Research suggests that a growing number of seniors continue to be sexually active, and in doing so, they stay healthier and happier. Although seniors are often hesitant to discuss intimate issues with their doctors, a new study suggests that older adults have been turning to online communities to get the answers and support they need from one another.

Sexual activity among older adults is commonplace—more than half of men and one third of women in their 70s, some married and some not, reported having sex at least twice a month in a 2015 study published in *Archives of Sexual Behavior.* (*Scientific American Mind* is part of Springer Nature.) But it can be complicated. Medical conditions that arise with advancing age, such as diabetes and heart disease, can affect sex drive and performance. Widows and widowers who start dating again later in life may not know how to protect themselves from sexually transmitted diseases or how to approach a new partner. Making matters worse, ageist stereotypes—such as the idea that seniors are "too old for sex"—can make it difficult for older adults to get answers.

A 2011 review of the research literature concluded that not only do older adults seldom raise questions about sex with their physicians but that their doctors are hesitant to bring up the topic. "The findings, literature and current media suggest that health care providers and staff in seniors' residential facilities and nursing homes themselves often ignore their clients' and residents' sexual health, needs and rights," explains Liza Berdychevsky, a social scientist at the University of Illinois at Urbana-Champaign.

In light of this concerning trend, Berdychevsky and her colleague Galit Nimrod, a communications researcher at Ben-Gurion University of the Negev in Israel, explored whether seniors get any sexual support from online forums. After reviewing nearly 700,000 messages posted in the span of a year to an international collection of online senior communities, they found approximately 2,500 posts dedicated to the discussion of sexual issues. Although that is less than 0.4 percent of all posts, some of these threads were hugely popular, with thousands of views, suggesting that a number of community members who were not participating in the discussions were nonetheless reading them. The researchers also saw evidence to suggest that these posts helped to answer users' questions and make them feel more comfortable about their evolving sexuality, according to a paper they published in June in the *Journal of Leisure Research.*

"The communities offer their members reassurance that they are not alone and that whatever they experience is faced by many others in their age group," Berdychevsky says, and the online forums provide "a channel for sharing their difficulties, gaining firsthand knowledge and exchanging advice." She and other investigators continue to emphasize the importance of better face-to-face communication about sex, especially in health care settings. Yet as more and more older adults around the world gain access to the Internet, their sex lives—and, it follows, general well-being—are better for it.

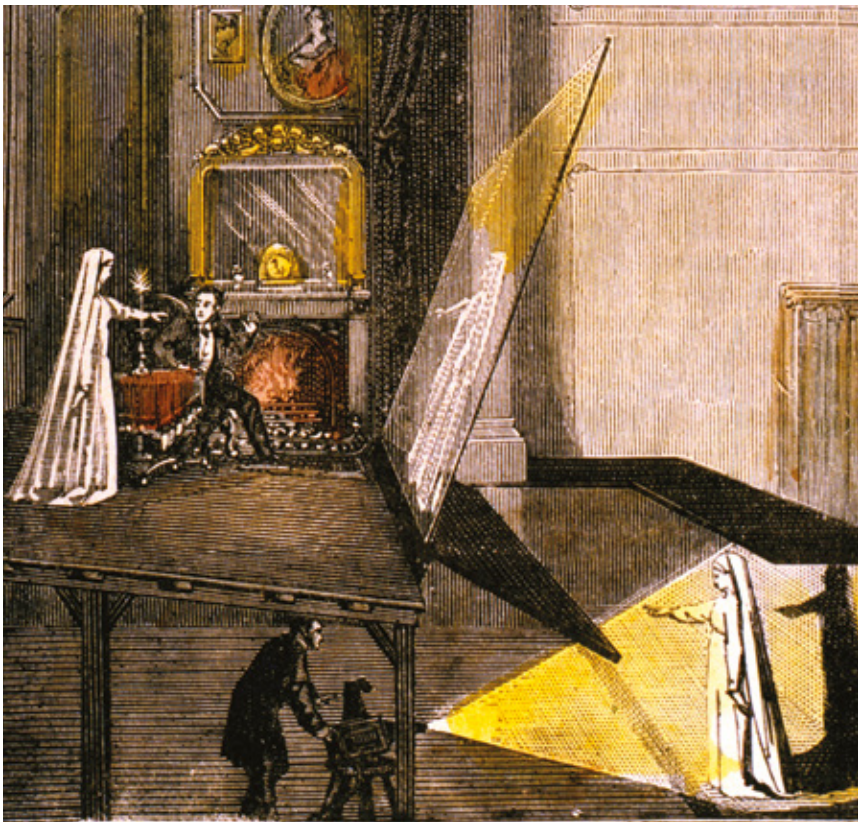
—*Melinda Wenner Moyer*

Victorian Theatrics

Nineteenth-century entertainment was a peculiar mix of technological innovation and supernatural thinking

On December 24, 1862, a new theatrical adaptation of Charles Dickens's fifth and last Christmas novella—his first being *A Christmas Carol*—premiered at the Royal Polytechnic Institution in London. In *The Haunted Man and the Ghost's Bargain*, an aging, gloomy, Scrooge-like chemistry teacher called Redlaw asks to have his memory erased. A ghostly doppelgänger grants him his wish but also curses anybody with whom he interacts to suffer the same fate.

Theatergoers attending this particular performance were in for a shock: instead of confronting the usual flesh-and-bone actor with a sheet over his head, Redlaw faced an incorporeal entity that materialized onstage, apparently out of thin air. Spectators were astonished.



The artist behind this illustration, published in the 1880s, took a few liberties. In reality, the actor below the stage must lie against a black inclined background to cast no shadow and correctly reflect on the glass. In addition, the pane is not a projection surface. The audience perceives the ghost as behind, not on, the glass—roughly where the apparition stands on the stage.

The play, which had not been performed in London for more than a decade, became an instant sensation. Enthralled audiences filled the Royal Polytechnic's 500-seat theater for 15 months straight, shelling out £12,000—or the equivalent of more than $2 million today.

The otherworldly apparition was a stage illusion that came to be known as Pepper's Ghost, the brainchild of Liverpool civil engineer Henry Dircks and Professor John Henry Pepper, a prominent London chemist and science popularizer. Dircks and Pepper's joint patent gave all the financial rights to the professor, and the two inventors fell out shortly after its issue over matters of credit and precedence.

But versions of their Ghost continue to delight audiences to this day. Look for Pepper's Ghost in Alfred Hitchcock's *The 39 Steps* or the James Bond flick *Diamonds Are Forever*. The same illusion was put to work in Disneyland's Haunted Mansion, where riders see specters materialize before them. These projections appear strikingly three-dimensional, in part because they retain many of the cues that inform our visual perception of depth in everyday life, such as size, shading and texture. And unlike a standard projection experience, such as what we see at a movie theater, there is no visible screen to tip us off that we are viewing a two-dimensional image on a flat surface. Instead the Pepper's Ghost illusion employs transparent surfaces so the image appears to be cast in thin air. (For more details, see "It's All Done with Mirrors," on page 20.)

A growing understanding of the visual sciences in Victorian times not only

BY SUSANA MARTINEZ-CONDE AND STEPHEN L. MACKNIK

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

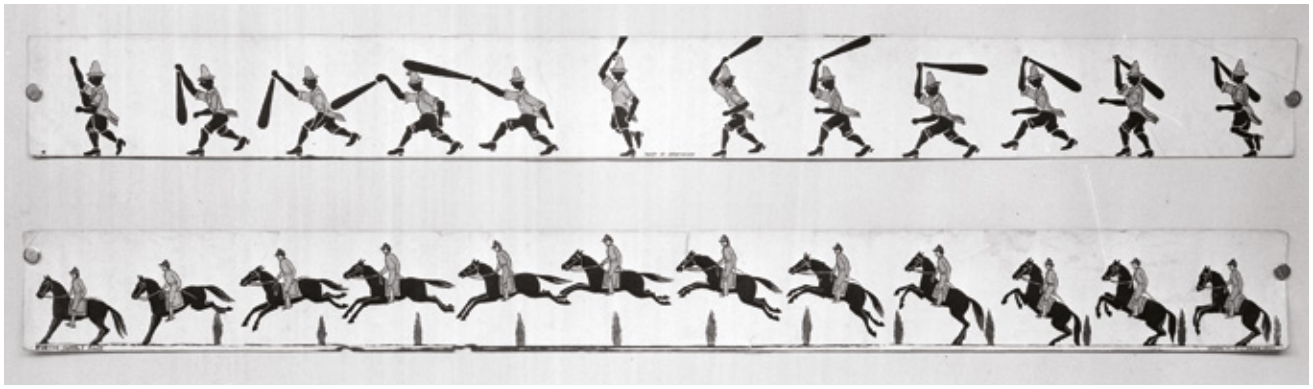
Send suggestions for column topics to **MindEditors@sciam.com**

AGE FOTOSTOCK (*illustration*); SEAN McCABE (*Martínez-Conde and Macknik*)

enhanced entertainment in the theater but also launched the development of early cinema. Contemporary filmmaking techniques, as well as their earliest predecessors, rely on a perceptual process discovered by Peter Mark Roget, best known for his famous *Thesaurus of English Words and Phrases*. In an 1824 presentation to the Royal Society of London, Roget revealed the "persistence of vision": the retina's ability to retain an image for $^1/_{20}$ to $^1/_5$ of a second after its disappearance. This phenomenon allows us to bridge the temporal gap between two consecutive static images of a moving object—think of two movie frames—and see continuous motion instead.

This article showcases the use of novel scientific and technical understanding to create unprecedented spectacles and theatrical illusions in Victorian society. **M**

BEFORE THE MOVIES



From 1833 to 1834, British mathematician William George Horner developed the zoetrope, a cylindrical device that sweeps images across the visual field as it turns, producing animation. One critical aspect of the zoetrope is that the images are periodically blocked, so that objects in them do not appear to continuously slide in and out of the scene. To further hide the sweeping of the objects, viewers may peer through a narrow slit. Modern movie projectors are a type of zoetrope, in which a flickering light turns off while the film advances to the next frame and then turns back on—projecting the image to the screen—only when each new frame is stationary and aligned with the previous one. Zoetrope technology led to modern television and computer-animation systems that update the image periodically without physically sweeping each separate image on and off the screen.

GHOSTBUSTERS!

The success of Pepper's Ghost with Victorian audiences underscores their double fascination with science and the supernatural. The 19th century was a time of extraordinary scientific and technical achievement—think of the telegraph, telephone, pasteurization and Charles Darwin's *On the Origin of Species* (1859). This fresh interest in science clashed with traditional religious beliefs but counterintuitively opened the door to a new kind of magical thinking: the Spiritualist movement, which held that people could communicate with the dead.

Spiritualism drew strength in part from recent scientific—and pseudoscientific—efforts. Animal magnetism (also known as mesmerism, after its founder Franz Mesmer) used techniques similar to those in modern hypnosis to allegedly reveal an individual's deepest thoughts. Sigmund Freud, the creator of psychoanalysis, took these claims as evidence of the subconscious. And some Spiritualists co-opted this idea of a subconscious, claiming that it was from this space that ghosts and spirits manifested.

Psychic and parapsychological research afforded spiritualism extra credibility. Séance mediums proliferated, offering customers the "tangible" supernatural evidence that churchgoing did not provide. In practice, of course, these séances were little more than elaborate performances, as Victorian magician John Nevil Maskelyne—inventor of the pay toilet—and Ehrich Weiss (aka Harry Houdini) revealed in a series of exposés. They kicked off the ongoing tradition among magicians to debunk such "paranormal occurrences."

Alongside séances, spirit photography, which claimed to capture ectoplasmic pictures of ghosts, also became popular. In reality, photographers manipulated the images after the fact, using ink or double exposure, among other techniques (the 19th-century equivalent of digitally altering pictures using Photoshop).

GETTY IMAGES (*zoetrope strips*); CORBIS (*spirit photography*)

IT'S ALL DONE WITH MIRRORS

Plain glass can be reflective or transparent, depending on how strong the light is on either side. And in certain lighting conditions, it can be both. This is the secret behind Pepper's Ghost.

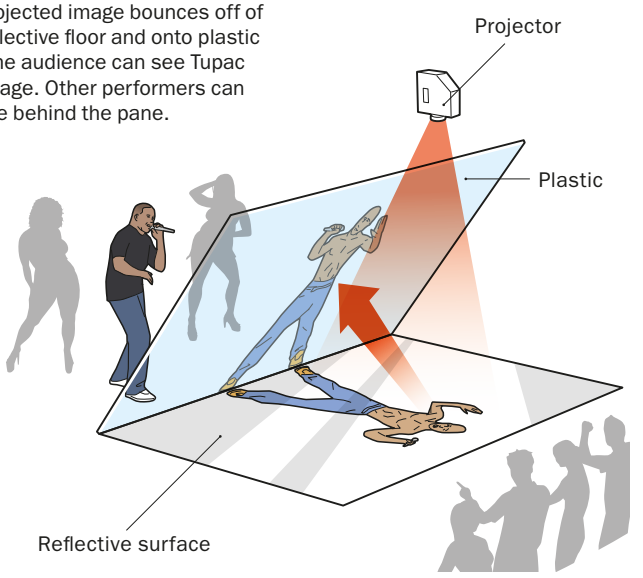
In 2012 a ghostly semblance of murdered rapper Tupac Shakur performed alongside fellow artists Snoop Dogg and Dr. Dre at the Coachella Valley Music and Arts Festival in California (*above*). What many spectators and reporters took to be a 3-D hologram of the rapper was in fact a 2-D image based on technology from the 19th century. Specifically, Tupac's projected image bounced off a reflective floor onto a plastic surface angled at 45 degrees—a design (*at right*) that recaptured the essence of Dircks and Pepper's innovative blueprint.

In the original 1862 arrangement at the Royal Polytechnic, the audience sat at the same level as the actors onstage, while the performer playing the ghost hid in the orchestra pit below. A large piece of glass was angled so that it could reflect a view of the pit toward the audience. When the lights were bright on the main stage and dark below, the reflection of the ghost stayed hidden. But when the lighting above dimmed and grew bright below, the reflection suddenly appeared. Space limitations under the stage allowed for reclining and sitting ghosts only. Later refinements permitted standing and walking ghosts.

Tupac: Not Live but in Concert

A 20th-century spin on a classic Victorian special effect

A projected image bounces off of a reflective floor and onto plastic so the audience can see Tupac onstage. Other performers can move behind the pane.



THE BIRTH OF FILM

Photographic and theatrical illusions gave way to the nascent film arts at the close of the 19th century. French magician Georges Méliès, who brought his conjuring background to moviemaking, pioneered cinema as entertainment (*above*). He also invented and adapted innovative special effects for film, such as the stop trick technique—in which objects and people in a movie scene change while the camera is off—to make actors disappear and reappear as, say, skeletons, among a myriad other illusions.

In 2011 Martin Scorsese's movie *Hugo* paid homage to Méliès's legacy. In one of the scenes, Ben Kingsley, playing Méliès, performs a levitation trick at the Robert-Houdin Theater in Paris (founded by renowned magician Jean-Eugène Robert-Houdin, from whom Houdini took his stage name). Méliès's assistant lies horizontally in midair, not thanks to CGI magic but to Victorian artifice unearthed by present-day illusionist Paul Kieve at Scorsese's request.

MORE TO EXPLORE

- **Explanation of an Optical Deception in the Appearance of the Spokes of a Wheel Seen through Vertical Apertures.** P. M. Roget in *Philosophical Transactions of the Royal Society of London,* Vol. 115, pages 131–140; January 1, 1825.
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- **Vision: Temporal Factors.** Stephen L. Macknik and Susana Martinez-Conde in *Encyclopedia of Perception.* Edited by E. Bruce Goldstein. SAGE Publications, 2010.
- **Theatre and Ghosts: Materiality, Performance and Modernity.** Edited by Mary Luckhurst and Emilie Morin. Palgrave Macmillan, 2014.

GETTY IMAGES (*photographs*); JASON LEE (*illustration*)

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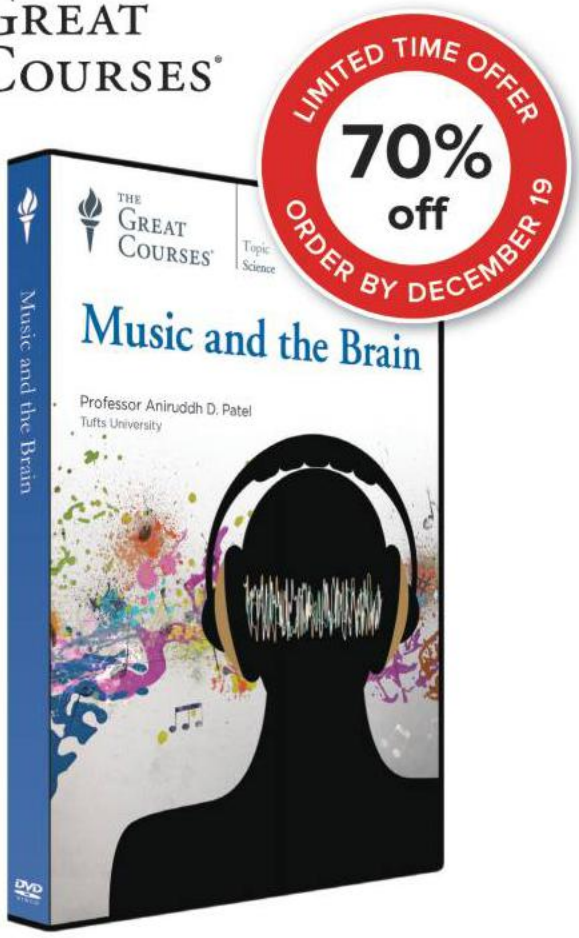

Are Humans Wired for Music?

Are we born with our sense of music? What gives mere tones such a powerful effect on our emotions? Why does music with a beat give us the urge to move and dance? How and why did musical behavior originate? Music is intimately woven into the fabric of our lives, yet we still ponder these deeply puzzling and provoking questions.

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LEARNING

The Positive Side of Peer Pressure

By not tapping the teenage fixation on social life, schools are missing an opportunity to motivate students

By Annie Murphy Paul

Parents of teenagers often view their children's friends with something like suspicion. They worry that the adolescent peer group has the power to prod its members into behavior that is foolish and even dangerous. Such wariness is well founded: statistics show, for example, that a teenage driver with a same-age passenger in the car is at higher risk of a fatal crash than an adolescent driving alone or with an adult.

In a seminal 2005 study, psychologist Laurence Steinberg of Temple University and his co-author, psychologist Margo Gardner, then at Temple, divided 306 people into three age groups: young adolescents, with a mean age of 14; older adolescents, with a mean age of 19; and adults, aged 24 and older. Subjects played a computerized driving game in which the player must avoid crashing into a wall that materializes, without warning, on the roadway. Steinberg and Gardner randomly assigned some participants to play alone or with two same-age peers looking on.

Older adolescents scored about 50 percent higher on an index of risky driving when their peers were in the room—and the driving of early adolescents was fully twice as reckless when other young teens were around. In contrast, adults behaved in similar ways regardless of whether they were on their own or observed by others. "The presence of peers makes adolescents and youth, but not adults, more likely to take risks," Steinberg and Gardner concluded.

Yet in the years following the publication of this study, Steinberg began to believe that this interpretation did not capture the whole picture. As he and other researchers examined the question of *why* teens were more apt to take risks in the company of other teenagers, they came to suspect that a crowd's influence need not always be negative. Now some experts are proposing that we should take advantage of the teen brain's keen sensitivity to the presence of friends and leverage it to improve education.

Not So Risky Business

In a 2011 study, Steinberg and his colleagues turned to functional MRI to investigate how the presence of peers affects the activity in the adolescent brain. They scanned the brains of 40 teens and adults who were playing a virtual driving game designed to test whether players would brake at a yellow light or speed on through the intersection.

The brains of teenagers, but not adults, showed greater activity in two regions associated with rewards (the ventral striatum and the orbitofrontal cortex) when they were being observed by same-age peers than when alone. In other words, rewards are more intense for teens when they are with peers, which motivates them to pursue higher-risk experiences that might bring a big

NATE KITCH

ANNIE MURPHY PAUL is a frequent contributor to the *New York Times, Time* magazine and Slate. Paul is author of *The Cult of Personality Testing* and *Origins,* which was included in the *New York Times* list of 100 Notable Books of 2010. Her next book, forthcoming from Crown, is entitled *Brilliant: The Science of How We Get Smarter.*

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payoff (such as the thrill of just making the light before it turns red). But Steinberg suspected this tendency could also have its advantages.

In his latest experiment, published online in August, Steinberg and his colleagues used a computerized version of a card game called the Iowa Gambling Task to investigate how the presence of peers affects the way young people gather and apply information. In this variant on the game, a computer would indicate a card from one of four decks, and players could decide to reveal that card or pass. Two of the decks would lead to an overall loss, and two would lead to overall gains. The experimenters told players that some decks were "good" and others "bad" but did not tell players which were which. Over the course of playing the game, participants gradually figured out which decks to return to and which to avoid. In Steinberg's study, which involved 101 adolescent males, researchers randomly assigned participants to play alone or in the presence of three same-age peers.

The results: Teens who played the Iowa Gambling Task under the eyes of fellow adolescents engaged in more exploratory behavior, learned faster from both positive and negative outcomes, and achieved better performance on the task than those who played in solitude. "What our study suggests is that teenagers learn more quickly and more effectively when their peers are present than when they're on their own," Steinberg says. And this finding could have important implications for how we think about educating adolescents.

Matthew D. Lieberman, a social cognitive neuroscientist at the University of California, Los Angeles, and author of the 2013 book *Social: Why Our Brains Are Wired to Connect*, suspects that the human brain is especially adept at learning socially salient information. He points to a classic 2004 study in which psychologists at Dartmouth College and Harvard University used functional MRI to track brain activity in 17 young men as they listened to descriptions of people while concentrating on either socially relevant cues (for example, trying to form an impression of a person based on the description) or more socially neutral information (such as noting the order of details in the description). The descriptions were the same in each condition, but people could better remember these statements when given a social motivation.

The study also found that when subjects thought about and later recalled descriptions in terms of their informational content, regions associated with factual memory, such as the medial temporal lobe, became active. But thinking about or remembering descriptions in terms of their social meaning activated the dorsomedial prefrontal cortex—part of the brain's social network—even as traditional memory regions registered low levels of activity. More recently, as he reported in a 2012 review, Lieberman has discovered that this region may be part of a distinct network involved in socially motivated learning and memory. Such findings, he says, suggest that "this network can be called on to process and store the kind of information taught in school—potentially giving students access to a range of untapped mental powers."

The Social Advantage

If humans are generally geared to recall details about one another, this pattern is probably even more powerful among teenagers who are hyperattentive to social minutiae: who is in, who is out, who likes whom, who is mad at whom. Their penchant for social drama is not—or not *only*—a way of distracting themselves from their schoolwork or of driving adults crazy. It is actually a neurological sensitivity, initiated by hormonal changes. Evolutionarily speaking, people in this age group are at a stage in which they can prepare to find a mate and start their own family while separating from parents and striking out on their own. To do this successfully, their brain prompts them to think and even obsess about others.

Yet our schools focus primarily on students as individual entities. What would happen if educators instead took advantage of the fact that teens are powerfully compelled to think in social terms? In *Social,* Lieberman lays out a number of ways to do so. History and English could be presented through the lens of the psychological drives of the people involved. One could therefore present Napoleon in terms of his desire to impress or Churchill in terms of his lonely melancholy. Less inherently interpersonal subjects, such as math, could acquire a social aspect through team problem solving and peer tutoring. Research shows that when we absorb information in order to teach it to someone else, we learn it more accurately and deeply, perhaps in part because we are engaging our social cognition.

And although anxious parents may not welcome the notion, educators could turn adolescent recklessness to academic ends. "Risk taking in an educational context is a vital skill that enables progress and creativity," wrote Sarah-Jayne Blakemore, a cognitive neuroscientist at University College London, in a review published last year. Yet, she noted, many young people are especially risk averse at school—afraid that one low test score or mediocre grade could cost them a spot at a selective university. We should assure such students that risk, and even peer pressure, can be a good thing—as long as it happens in the classroom and not the car. **M**

MORE TO EXPLORE

- **The Developing Social Brain: Implications for Education.** Sarah-Jayne Blakemore in *Neuron,* Vol. 65, No. 6, pages 744–747; March 25, 2010.
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MACHINE LEARNING

Do Androids Dream?

The search to understand how artificial neural networks process images yields insights and a trippy brand of beauty

> *Most of the afternoons I would pass looking out at the pasture. I soon began seeing things. A figure emerging from the birch woods and running straight in my direction. Usually it was the Sheep Man, but sometimes it was the Rat, sometimes my girlfriend. Other times it was the sheep with the star on its back.*
>
> —Haruki Murakami, *A Wild Sheep Chase,* 1982

Artificial intelligence has been much in the news lately, driven by ever cheaper computer processing power that has become effectively a near universal commodity. The excitement swirls around mathematical abstractions called deep convolutional neural networks, or ConvNets. Applied to photographs and other images, the algorithms that implement ConvNets identify individuals from their faces, classify objects into one of 1,000 distinct categories (cheetah, husky, strawberry, catamaran, and so on)—and can describe whether they see "two pizzas sitting on top of a stove top oven" or "a red motorcycle parked on the side of the road." All of this happens without human intervention. Researchers looking under the hood of these powerful algorithms are surprised, puzzled and entranced by the beauty of what they find.

BY CHRISTOF KOCH

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

Springtime for A.I.

How do ConvNets work? Conceptually they are but one or two generations removed from the artificial neural networks developed by engineers and learning theorists in the 1980s and early 1990s. These, in turn, are abstracted from the circuits neuroscientists discovered in the visual system of laboratory animals. Already in the 1950s a few pioneers had found cells in the retinas of frogs that responded vigorously to small, dark spots moving on a stationary background, the famed "bug detectors." Recording from the part of the brain's outer surface that receives visual information, the primary visual cortex, Torsten Wiesel and the late David H. Hubel, both then at Harvard University, found in the early 1960s a set of neurons they called "simple" cells. These neurons responded to a dark or a light bar of a particular orientation in a specific region of the visual field of the animal. Whereas these cells are very particular about where in visual space the oriented line is located, a second set of "complex" cells is less discerning about the exact location of that line. Wiesel and Hubel postulated a wiring scheme to explain their findings, a model that has been enormously influential. It consists of multiple layers of cells—the first layer corresponds to the input cells that carry the visual information as captured by the eyes. These cells respond best to spots of light. They feed into a second layer of neurons, the simple cells, that talk in turn to a third layer of neurons, the complex cells.

Each cell is, in essence, a processing element or unit that computes a weighted sum of its input and, if the sum is sufficiently large, turns the unit's output on; otherwise, it remains off. The exact manner in which the units are wired up determines how cells in the input layer that respond to edges of any orientation are transformed into simple cells that care about a particular orientation and location and then into units that discard some of that spatial information. Subsequent discoveries of neurons in a region of the

LIZ TORMES

A technique called Inceptionism, developed by Google scientists, is used to explore the workings of neural networks. Available as open-source code called DeepDream, it morphs ordinary photographs into bizarrely beautiful images in which eyes, insects and odd creatures emerge from the scene.

monkey visual cortex that switches on for views of faces of monkeys or people reinforced such thinking—visual processing occurs within a hierarchy of processing stages in which the information flows upward, from units that care about low-level features such as brightness, orientation and position to units that represent information in a more abstract manner, such as the presence of any given face or a specific one, such as that of Grandma. Appropriately, this cascade of processing layers is called a feed-forward network.

ConvNets also operate like these specialized networks. A first layer of units represents the raw images, whereas subsequent layers extract more and more abstract features. The last output layer may consist of 1,000 units, each representing one of the abovementioned visual-object categories. It effectively decides which object is present in the image. Other signals encode the network's confidence in its final decision.

The modern descendants of these feed-forward networks are bloated, sporting 20 or more layers. Each processing layer has its own wiring scheme, specifying which unit influences which other unit and how strongly it does so. The entire network can have 10 million or more parameters called weights associated with it. And each one must be assigned some numerical value, positive or negative. These legions of numbers cannot be intuited or guessed; they have to be set by hand, an impossible task.

That is where machine learning comes in. Setting these parameters occurs during a learning phase in which the network is shown a million or more pictures of individual objects, together with labels, say, "husky" or "cheetah." Think of Mom showing her toddler a picture book, pointing at a drawing and saying, "Dog." After each such presentation, the network makes a guess based on some initial random setting of its weights.

These are then slightly adjusted to reduce the inevitable mismatch between the output of the network—its guess about what it is looking at—and the correct label. This process repeats over, and over, and over. Supervised learning (the nerdy term is back-propagating the error, or back-prop) is enormously expensive computationally and only became feasible because of the widespread use of so-called graphical processing units developed to support video gaming. Once the training is complete, the network is frozen—it halts the labeling exercises—and can now process novel images, ones it has not previously seen, and can guess their identity, often with near human accuracy.

Machine learning is all the rage in academia and industry, with teams of applied mathematicians and computer scientists competing to develop ever smarter algorithms for optimizing performance.

> CONVOLUTIONAL NETWORKS CAN CORRECTLY IDENTIFY YOUR VACATION PIC AS SHOWING A HUSKY OR A BEGONIA, BUT THEY ALSO **ARRIVE AT NONSENSICAL CONCLUSIONS.**

What Are These Networks Really Doing?

Though relatively simple, ConvNets can yield unexpected surprises. Yes, they can correctly identify your vacation pic as showing a husky or a begonia, but they sometimes also arrive at nonsensical conclusions. A case in point is work by Anh Nguyen and Jeff Clune, both at the University of Wyoming, and Jason Yosinski of Cornell University. To shine light inside the black box of the network, Clune, a computer science professor, and his students developed techniques to dis-

Getting Real

A neural network builds up an image layer by layer.

Processing Layer 1 **Processing Layer 3** **Processing Layer 4**

A deep-learning neural network comes to recognize a tiger by first observing pixels at one network layer that represent lines of color in the animal's fur. It gradually constructs a representation of increasingly abstract features—an eye and later a head—at higher layers of the network.

cover pictures that would evoke strong activation from particular units in a trained ConvNet, asking, "What does this unit really like and want to see?" And how similar would these images be to the pictures that the network encountered during its infancy, when it was being trained? The team started with random images and "evolved" them repeatedly until the network decided, with high confidence, that they were a cheetah, or a handheld remote control, or another visual-object category it had been trained on. The expectation was that the evolutionary algorithm would discover images that most faithfully represented cheetahness, the Platonic idea of a cheetah.

To their surprise, the resultant images were often completely unrecognizable, essentially garbage—colorful, noisy patterns, similar to television static. Although the ConvNet saw, with 99.99 percent confidence, a cheetah in the image, no human would recognize it as a big and very fast African cat. Note that the computer scientists did not modify the ConvNet itself—it still recognized pictures of cheetahs correctly, yet it strangely also insisted that these seemingly noisy images belonged to the same object category. Another way to generate these fooling images yielded pictures that contain bits and pieces of recognizable textures and geometrical structures that the network confidently yet erroneously believed to be a guitar. And these were no rare exceptions.

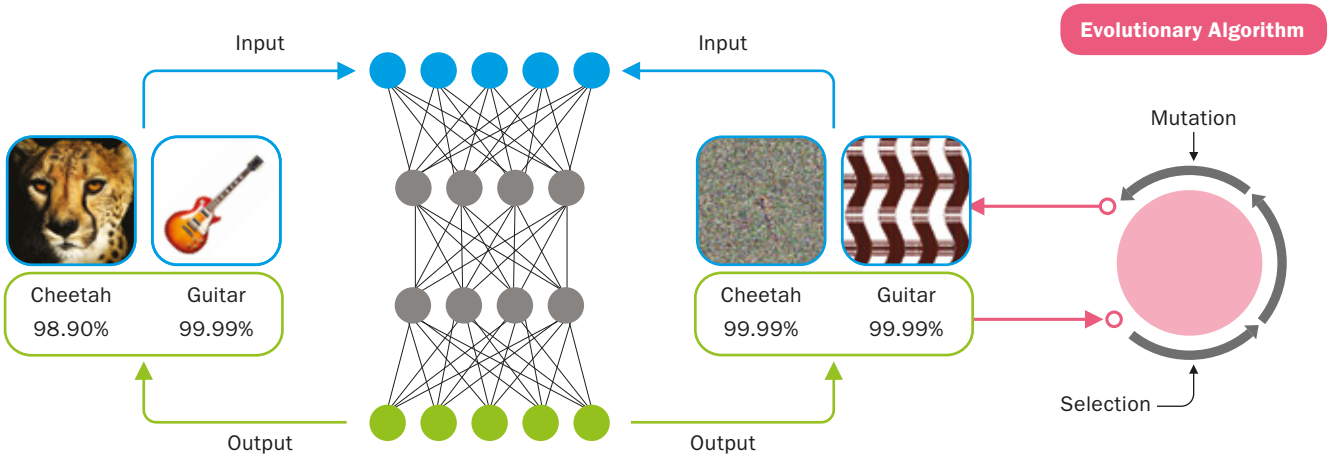
I suspect that if the same image manipulations were to be carried out while recording from the face cells deep inside the visual brain, this procedure would not converge to such nonsensical images but would capture something essential about the nature of faces.

> OVER THE NEXT DECADE A PROPERLY FORMULATED THEORY OF MEANING MAY BRIDGE THE GAP BETWEEN HOW **MACHINES AND HUMANS "SEE" IMAGES.**

These faux images highlight a large gap between the way people and computers understand visual objects. By watching a cheetah in a zoo or seeing one chase down a gazelle in a nature documentary, we build up an internal representation of these cats that allows us to describe them. If we were forced to, most of us could even draw a cartoon of these graceful animals and specify how they differ from lions or house cats. But computers know nothing of this context. All they have been given are 100 cheetah photographs and a gazillion noncheetah pictures. Without knowing anything about cats—that they have legs, paws, fur, pointed ears, and so on—the network has to figure out what features in the few training images are characteristic of the class of objects known as cheetahs. These same features can also be found in all kinds of other misleading images.

This gap had been pointed out for 30 years by American philosopher John Searle in his famous "Chinese room" argument, in which a non-Chinese speaker is able to provide coherent answers to questions posed in Chinese by following a set of carefully laid-out instructions in English to manipulate Chinese characters, even though the individual has no idea what they mean. Searle invented this powerful thought experiment to support his claim that computers, like

GETTY IMAGES



A ConvNet recognizes a cheetah or guitar with a high degree of confidence (*left*), but it can also be fooled if its input image is subject to further processing by an evolutionary algorithm. It might then misidentify a nonsensical image as a cheetah or a guitar (*right*).

SOURCE: "DEEP NEURAL NETWORKS ARE EASILY FOOLED: HIGH CONFIDENCE PREDICTIONS FOR UNRECOGNIZABLE IMAGES," BY ANH NGUYEN ET AL. PRESENTED AT THE 2015 IEEE CONFERENCE ON COMPUTER VISION AND PATTERN RECOGNITION, BOSTON; JUNE 7–12, 2015 (*neural network* and *patterns*); © ISTOCK.COM (*cheetah* and *guitar*)

the individual in the Chinese room, can never understand anything—they simply follow a set of instructions that makes them appear to be intelligent. That is still true today. But over the next decade machines will become more sophisticated, and it will be more difficult to fool them. The gap between them and us will lessen. Indeed, quite unlike Searle, I do believe that a properly formulated theory of meaning, closely allied to a theory of consciousness, will permit us to ultimately bridge this gap—and truly intelligent machines will then emerge.

Trees Growing Bird Heads

If you are somebody who believes that art and algorithm have nothing but a first letter in common, consider a different way to understand the innards of these networks. In a June 17 blog post, three software engineers, Alexander Mordvintsev, Christopher Olah and Mike Tyka, all at Google, describe a technique termed, in a stroke of marketing genius, Inceptionism, a reference to the popular 2010 psychological science-fiction thriller. The programmers present a starter image to a fully trained machine-learning network and then focus on the artificial neurons in a particular layer between the input layer—equivalent to the retina in an eye—and the final output layer that categorizes an object. The engineers then tweak the input image to maximize the response of the units they are attending to. If they focus on a set of Hubel-and-Wiesel-like units that extract horizontal edges, adding horizontal lines to the original image will enhance their internal response. Or if they focus on units in the upper layers of the network that code for eyes, then inserting eyes into the image will maximize their firing rate. The image is slowly morphed; think of it as controlled hallucination. When focusing on bird units in the upper layers, Inceptionism begins to image birds and superimposes them onto the original images. This turns on the bird units, which further drive the algorithm to enhance the saliency of birds in the image, and so on. Just search online for "Inceptionism," and you will see what I mean. Not surprisingly, the June post has gone viral.

These images are bizarre, strange yet compelling, and often quite pleasing. In an empty sky, birds become visible. Felines are superimposed onto the faces of people in a crowd. A gigantic fish comes to life in the heavens. Patterns imbued with meaning appear in leaves. Castles can be dimly perceived, hovering in the background over an otherwise empty desert landscape. Deep networks go to sleep and dream. It's magical.

Many people have noted the remarkable resemblance between these images and hallucinations produced by tripping on LSD, mescaline or psilocybin mushrooms. In response to the explosion of interest, Google has released open-source code, named DeepDream, to generate such images and assemble them into movies (see http://bit.ly/1FcTca2). For those of us who do not program, a start-up will, for a small fee, modify any image you supply.

For me, as a card-carrying neuroscientist, what is most tantalizing is the architectural resemblance between the way brains and ConvNets behave. Left to their own devices, what will ConvNets dream about? Electric sheep? Or perhaps a cross between a pig and a snail that shimmers with a psychedelic iridescence? M

MORE TO EXPLORE

- **Deep Neural Networks Are Easily Fooled: High Confidence Predictions for Unrecognizable Images.** Anh Nguyen et al. Presented at the 2015 IEEE Conference on Computer Vision and Pattern Recognition, Boston; June 7–12, 2015.
- More examples of images that fooled the computer can be found at **http://evolvingai.org/fooling**

THINKING ABOUT **WHAT-IFS** ISN'T JUST AN EXERCISE IN WHIMSY. IT HELPS US LEARN FROM OUR EXPERIENCES—BOTH TO PREPARE FOR THE FUTURE AND TO MAKE SENSE OF THE PAST

BY FELIPE DE BRIGARD

ILLUSTRATIONS BY COLIN HAYES

MY friend Bertrand can easily imagine never meeting his wife, Laura. The circumstances were peculiar. He was visiting an unfamiliar town for work, not too far from his home. An acquaintance who happened to be there at the same time invited him out to a dance club in yet another neighborhood he otherwise wouldn't have visited. At the last minute he decided to go.

He arrived late, so he had to wait in line in the wintry cold. Next to him stood a group of people waiting for a cab, including Laura. He and Laura both cupped their hands and blew warm air into them at the same time. "It is cold," they said in unison, then laughed. They chitchatted briefly. A cab soon arrived, and Laura left. Bertrand couldn't get her off his mind.

Early the next morning Bertrand was sitting on a bench, waiting for a bus that would take him home. It was running late. In front of him a bike stopped sharply at a red light—it was Laura. He ran up to her, and she recognized him immediately. Bertrand convinced her to exchange phone numbers with him. They married two years later and have been together for nine years. They recently welcomed their first child.

When Bertrand tells this story, it is impossible not to wonder what would have happened if his friend had not been in town that day, or if Bertrand had decided to go to the club earlier, or if the bus had been on time, or if the light hadn't turned red so Laura would have just zoomed by, unnoticed. Would they still have met? Would they be married today? The human tendency to mentally replay past events while varying one or two critical details, letting the scenario unfold for a few seconds into the mysterious realm of the what-if, is known as counterfactual thinking because it involves mulling over something that is not true or is "contrary to fact."

Imagining alternative scenarios can imbue the past with deeper meaning and emotion.

We use our imagination in many ways. Novelists rely on it to dream up plots, characters and scenes. Artists use it to conjure new works. Children entertain themselves by weaving fantastical worlds in their minds. For adults, however, one of the most common—and underappreciated—uses of imagination is counterfactual thinking. We dip into alternative realities with a frequency and ease that suggest this habit is core to the human experience. Yet imagination has long been seen as random, obeying no principles and resting outside the scope of science. That view began to change in the early 1980s, after cognitive scientist Douglas R. Hofstadter offered a tantalizing insight. Hofstadter suggested that the mind has a series of what, in a 1982 *Scientific American* column, he called "fault

FAST FACTS
IMAGINE THAT

1. We routinely and automatically reflect on our experiences by imagining ways things could have gone differently, a habit known as counterfactual thinking.
2. These thoughts often let us learn from our mistakes and triumphs to prepare us for the future. Other times, however, they help us come to terms with our past.
3. Imagining alternative versions of a memory can change its emotional intensity, as well as our judgments of it.

PRECEDING PAGES: © ISTOCK.COM

lines" where things can shift. When we muse about the different ways an event might have unfolded, we tend to be predictable: we alter certain parameters but not others. Ever since Hofstadter's insight, cognitive scientists have been mapping these fault lines and discerning their purpose. Imagination, it seems, helps us transcend the reality of the immediate present to come to grips with our past and prepare for the future. Exploring the unreal may be an important step in finding meaning in, and shaping the narrative of, our everyday lives.

Playing with Reality

In the spirit of Hofstadter's conjecture, Nobel Prize–winning psychologist Daniel Kahneman, now at Princeton University, along with Amos Tversky of Stanford University and Dale Miller, now at Stanford, conducted pioneering studies in the 1980s to investigate whether people behaved predictably when imagining variants of common events. In one of these studies, by Kahneman and Tversky, participants read a vignette depicting the tragic story of a teenager who, while driving under the influence of drugs, crashed into a man's car, killing him instantly. The story is full of "junctures": causally relevant events that, had they been different, would have prevented the accident from occurring. When Kahneman and Tversky asked their subjects to revise the story so as to avoid the accident, they found that participants were overwhelmingly more likely to imagine undoing rare or abnormal events (such as deciding to take an unusual route) rather than ordinary, frequent events (such as leaving the office at a regular hour).

Ever since, some psychologists have engaged in a kind of cognitive geology (call it psysmology?) to map the fault lines of our imagination. We have learned, for example, that when people imagine alternatives to a given event, they are more likely to mutate actions rather than inactions, causes rather than background conditions and controllable events over uncontrollable ones. Our wishful thinking also tends to focus on altering recent events over bygone ones and morally or socially unacceptable occurrences over less offensive ones. Taken together, these findings supported an explanation proposed by Kahneman and Miller in 1986, called norm theory. The idea was that we derive from our experiences a series of templates, or "norms," against which we compare imagined alternative realities. Because in day-to-day life we are more likely to arrive at a destination early or late than we are to show up and find it closed, we are more inclined to imagine Bertrand never meeting Laura because he waltzed into the venue without waiting in line rather than because he found the club shut down.

Not every facet of norm theory has stood the test of time, but the gist of it—that there is some order to the way people imagine scenarios—has remained. In fact, as psychologist Ruth M. J. Byrne of Trinity College Dublin has suggested, our imagination may closely resemble rational thinking, which is highly predictable and subject to relatively strict rules. Just as there is a logic to how we reason, there is a logic to what we imagine.

Preparing for the Future

Psychologists figured out fairly early on that counterfactual thinking serves a purpose—it girds us for the future. Most of our counterfactual thoughts occur when we fail to obtain a desired goal: passing an exam, scoring a goal, finishing a task on time. And usually when we fail, we imagine undoing a certain action and achieving the desired effect: "Had I gone to bed earlier last night, I wouldn't have slept through the exam this

Picturing better outcomes (upward counterfactuals) can help us learn from our mistakes.

morning." These kinds of counterfactuals, in which we imagine a better alternative to a bad event, are called upward counterfactuals (the dreamed-up scenario is better than reality), and they tend to elicit negative feelings, predominantly regret. When we contemplate worse versions of good outcomes ("Had I missed that shot we would have lost the game"), we are entertaining downward counterfactuals, which tend to be associated with positive feelings, such as relief. Considering other ways things could have gone might give us a leg up the next time we face a similar task.

For example, in one 1994 study by psychologists Neal J. Roese of Northwestern University and James M. Olson of the University of Western Ontario, participants tackled several anagrams, mostly unsuccessfully. Half of them were asked to imagine what they might have done differently. When the participants again saw a similar set of puzzles, only the individuals who had reflected on other approaches performed better on the new anagrams.

Yet letting your imagination run wild isn't always productive. In 2003 psychologists Keith Markman of Ohio University and Matthew N. McMullen of Montana State University Billings revealed that upward counterfactuals can also elicit positive feelings. For example, a person who considers what it might have taken to avoid bombing a test might decide that failure was acceptable, rather than feeling regret and a desire to try harder next time. Likewise, downward counterfactuals can produce negative feelings, too. Consider the case of Kim Stroka, then a flight attendant for United Airlines who was scheduled to work on the ill-fated Flight 93 on September 11, 2001. The day before, she switched shifts—a move that saved her from perishing when the plane crashed in a field in Pennsylvania. Yet Stroka became haunted by downward counterfactual thoughts, which led her to seek treatment for post-traumatic stress disorder. She sought workers' compensation for her stress, but United fought back. An appellate court eventually ruled that although the plane crash may well have been the cause of her PTSD, her condition was not the result of an accident that occurred in the course of her workday. Even so, her downward counterfactual rumination was severely debilitating.

We also generate counterfactual thoughts about events that we know are never going to happen again—another strike against the idea that this form of thinking always prepares us for the future. I have a friend, Peter, who one day had a spirited argument with his father. His dad stormed out of the door, hopped in his car and drove up the road, only to fatally crash into a truck after failing to notice a red light at a busy intersection. Peter cannot help but imagine how things would have turned out if only he hadn't upset his dad or if he had urged him to calm down before driving away. Or consider the case of Anastasia, a young gymnast who repeatedly undoes in her imagination the terrible mistake that left her paraplegic.

Why would Peter's imagination so constantly and frequently slip into these alternative worlds? Is it because he's rehearsing for the next time he'll talk to his dad? That can't happen. Maybe he's doing it for the next time he faces a similar

Dwelling on what might have gone wrong (downward counterfactuals) can bring relief, but sometimes it becomes a haunting fixation.

THE AUTHOR

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situation with a loved one. But then what about Anastasia? She won't be able to move again, much less do gymnastics. What kind of future event is she planning to improve on? Perhaps the reason these cases appear puzzling is because we are thinking about their functional benefits in the wrong way: we may not always engage in counterfactual thinking to anticipate the future—perhaps we also do it to work through what has already happened.

Making Sense of Memories

We spend an enormous amount of time reminiscing about the events of our lives. Sometimes we do so in solitude; other times we discuss them with friends and loved ones. And we do more than replay past experiences unchanged. We ponder them, draw connections between events and, of course, imagine counterfactual alternatives.

Whenever Bertrand tells the story of how he met Laura, listeners inevitably start imagining scenarios in which they fail to meet. It is common to hear them follow their counterfactual thoughts with expressions such as "It was meant to be!" or even "It was destiny!" What happens next is also interesting: Bertrand and Laura hold hands or look at each other lovingly. Psychologist Adam Galinsky, now at Columbia University, along with Roese, Katie Liljenquist, now at Brigham Young University, and Laura Kray of the University of California, Berkeley, thinks counterfactual thoughts might enhance the importance we attach to past events.

To test this hypothesis, in 2010 Kray and her co-workers asked participants to write a short essay about a meaningful event in their life (such as getting into college). Next, half of the participants were instructed to describe all the ways things could have turned out differently. People who did so reported, on various scales (one to seven for the essays about college), that the past experience was more meaningful or significant to them than did individuals who did not engage in counterfactual simulation. The psychologists got a similar result in a follow-up experiment, in which they compared participants who engaged in counterfactual thinking with people who mentally replayed the events exactly as they had occurred. Imagination made the outcome seem almost destined to happen.

These mental exercises may serve an even more general and powerful role. Engaging in counterfactual thinking about our past may actually improve our well-being. In 2013 a study by Samantha Heintzelman, then a psychology graduate student at the University of Missouri, and her colleagues compared

Wishful thinking follows predictable patterns. It focuses on reversing rare, rather than ordinary, actions.

participants who imagined alternative versions of the events that led up to either their own birth or the election of Barack Obama. Both groups then answered questions about how meaningful and satisfying they found their life. The people who dreamed up stories relating to their birth reported higher ratings of well-being, purposefulness and satisfaction than did participants who mulled variations on Obama's election.

These results strongly suggest that engaging in counterfactual thinking about past events can influence our personal narrative. But how? Recent clues are emerging from a different line of research, on a related cognitive faculty: memory. For decades researchers thought that once a memory was established—consolidated—it remained fixed, unchanged. Recent discoveries have shown, however, that when we recall a memory, it becomes

We asked readers to tell us about their biggest what-ifs. Read a selection at **www.ScientificAmerican.com/WhatIfMoments**

prone to modification, until it returns to mental storage in a reconsolidated form. When you imagine alternative versions of a memory, the original recollection gets updated and sometimes tweaked. The next time the memory gets called up, some of its content might have been "edited."

Karl Szpunar, now at the University of Illinois at Chicago, Daniel Schacter of Harvard University and I started to explore the idea of using imagination to edit memories after we obtained a striking result a couple of years back. We had asked participants in one of our studies to engage in counterfactual thinking about past personal events while we scanned their brain activity in a functional MRI machine. Some of their imaginings were more plausible, others more fanciful. We noticed that when a person envisions more likely alternatives to a personal anecdote, his or her brain behaves very much as if it was remembering, whereas implausible counterfactuals do not produce that pattern of activity.

Pondering how things might have gone badly can elicit joy, relief and satisfaction.

We started thinking that there must be some important connection between remembering and imagining believable, as opposed to far-fetched, counterfactuals. So we followed up on this idea using a well-known method for making an event seem more likely to a person: repetition. Previous research has shown that when people repeatedly imagine something that might happen in the future—such as their getting a promotion at work or a state revoking a certain law—that scenario begins to seem more realistic.

In this study, published in 2013, participants again conjured different versions of some past events. Our subjects then reimagined half of those counterfactuals three times. A day later they came back to the laboratory and reimagined one last time all the counterfactuals they had created. We reached a counterintuitive result: repeatedly simulating those false versions of reality led people to think that they were *less* plausible than counterfactuals they simulated only once. Imagining the future, for which we lack strong templates (per Kahneman and Miller's norm theory), and reworking the past, for which a clear norm does exist—namely our actual memory—obey different rules. We interpreted this finding as suggesting that imagining around a memory helps us to come to grips with the past. To avoid wallowing in regret, say, our brain downplays repeated what-ifs about bygone times. As a result, you spend less time mulling them over, and you settle into a sense of acceptance.

Unfortunately, this pattern doesn't hold for everyone. Individuals with depression and anxiety may suffer from a tendency to mentally rehearse, over and over, the same imaginary alternative to a past experience. Several studies have shown that this habit is not only strongly associated with anxiety and depression but also is one of these disorders' most debilitating traits. Because sufferers are incapable of banishing such unwanted thoughts, they are less able to move forward with their plans.

Tinkering with Emotions

At this point, the question seems obvious: What makes certain kinds of counterfactual simulations beneficial and others harmful? Inklings of an answer come from recent proposals looking at real-world situations in which imagination and autobiographical recollection interact. One such situation is

Revisiting the what-ifs of a memory again and again can alter it in ways that enhance its emotional power.

psychotherapy. Earlier this year psychologists Richard Lane, Lee Ryan and Lynn Nadel, all at the University of Arizona, and Leslie Greenberg of York University in Ontario theorized that the most effective psychological therapies—in particular, cognitive-behavior therapy—leverage the power of imagination to modify harmful memories. They suggest that a therapist helps a patient create an imaginative context in which the client can modify the emotional content of memories to edit the past and remove its sting.

In the past year, in collaboration with memory researchers Peggy St. Jacques of the University of Sussex in England and Schacter, I have explored the effects of reactivating a memory while pondering its what-ifs. Though preliminary, our results suggest that when we visit a memory, the intensity of the original emotion tends to weaken the more often you remember it. That is, negative memories deliver less of a punch the next time around, and positive memories lose some of their sheen. But remembering an event while imagining a different version of it tends to preserve its original intensity: negative memories feel just as bad the next time, and positive memories continue to bring joy. We will need to explore carefully the relation between imagination, emotion and memory to make the most of it in a therapeutic context. Suffice it to say, for now, that imagination interferes with the changes that typically befall emotional memories.

Returning to the mundane circumstances in which counterfactual thinking and autobiographical memory collide and to my friend Bertrand's improbable love story, consider the conditions in which Bertrand tends to revisit the events that led up to meeting Laura. He does so usually in the presence of his wife, surrounded by friends or family, in social situations in which memory and imagination intertwine. The result of this nearly ritualistic conversation seems to be inevitably the same: both smile and gaze at each other fondly, and you can almost see their relationship growing stronger.

As these studies suggest, the more Bertrand and Laura imagine how the improbable events preceding their exchanging phone numbers could have turned out differently, the more likely they are to think of that moment as bound to happen. The act of remembering each event while imagining how easily it could have gone otherwise preserves the intensity of the emotion of the original memory—and who wouldn't want to preserve the happiness of such moments, untainted? So maybe here is the reason our mind wanders into possible what-ifs so often and so naturally: imagination not only helps us plan for a better future and ease the burden of our personal past. It may also help our memory preserve those emotions we most want to keep. **M**

MORE TO EXPLORE

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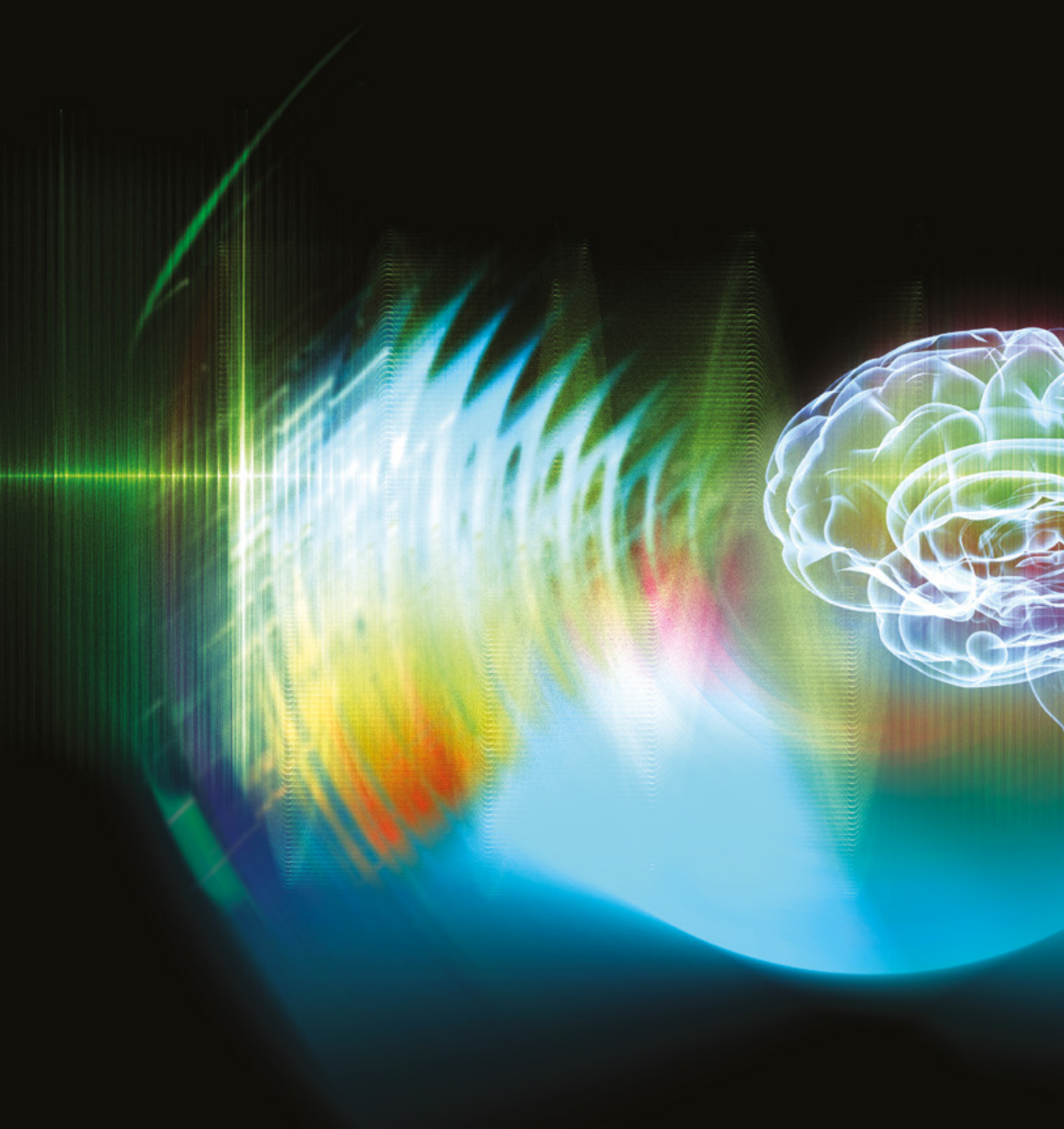

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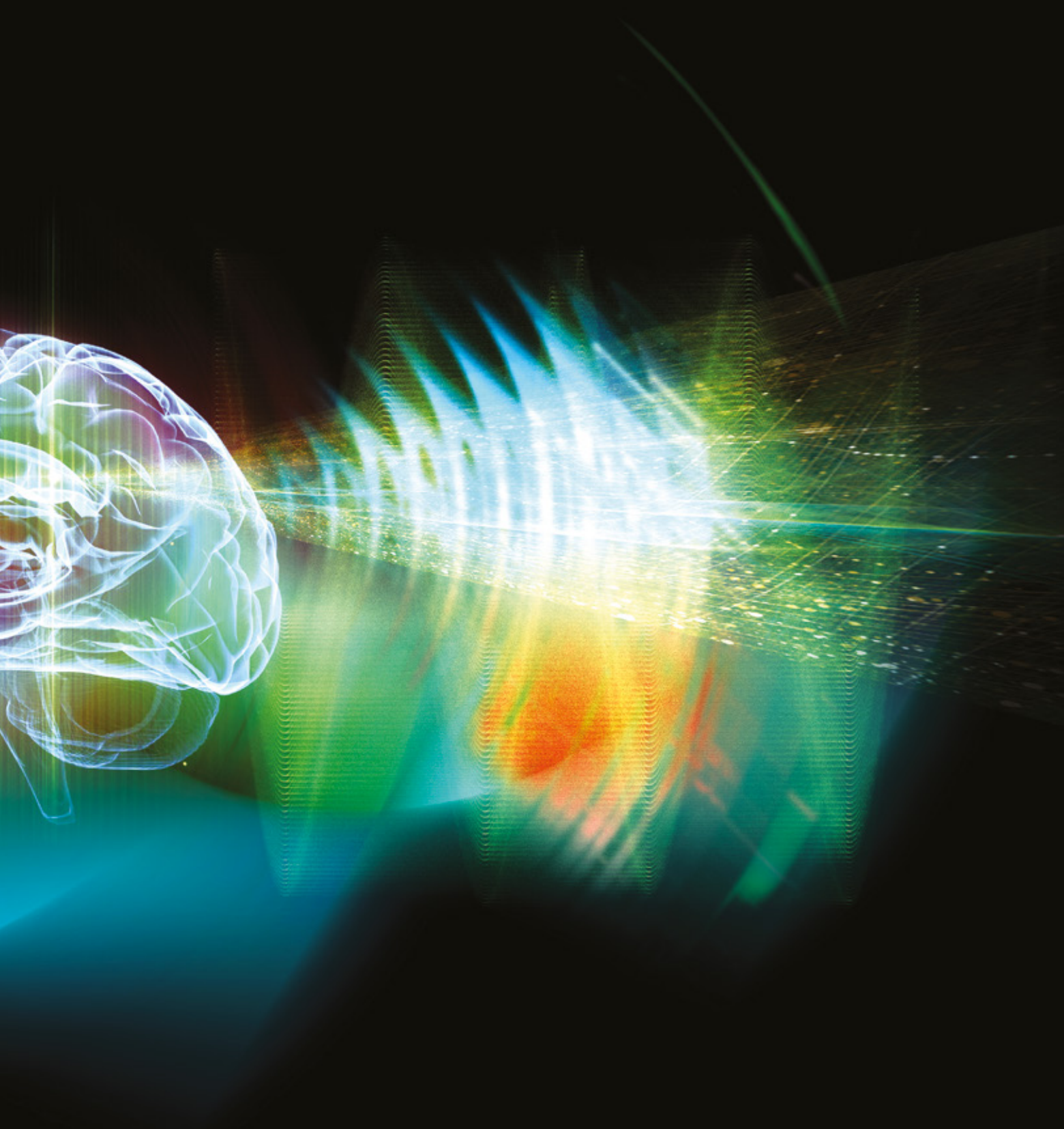


Surgeons can now operate deep within the brain using focused beams of ultrasound, ushering in a new era of faster, safer, incision-free treatments

By Stephen J. Monteith, Ryder Gwinn and David W. Newell

Illustration by **TATIANA PLAKHOVA**

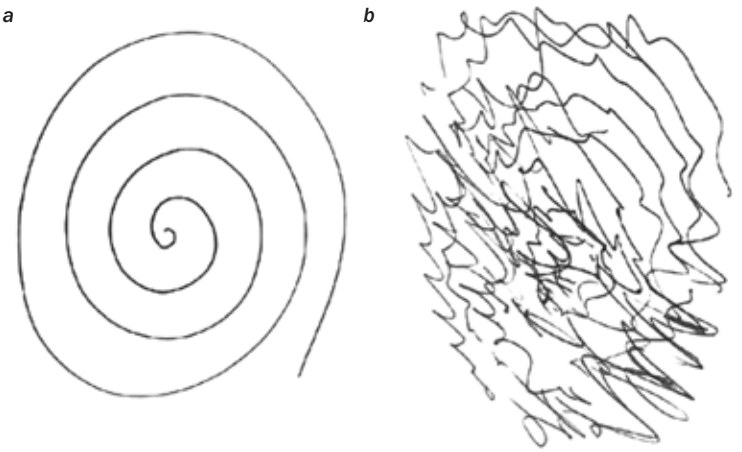
Carol Aldrich first noticed a slight tremor in her right hand when she was in her early 50s. Working for an optometrist in Port Townsend, Wash., a picturesque town on the Olympic Peninsula, Aldrich routinely performed delicate work with her fingers—replacing broken eyeglass lenses and repairing frames. At least initially, her tremor would come and go, leaving her sometimes unable to manage tiny screws and fragile settings. "I just thought I had had too much coffee," the mother of three recalls.

Gradually, though, her shaking grew more persistent. "After a while, it was with me all the time," Aldrich says. She visited her doctor who diagnosed essential tremor, which today is the most common movement disorder, found in about 5 percent of people older than 64 years worldwide. The cause of the condition is unknown, but it often runs in families. Its hallmark tremors are typically small, rapid, back-and-forth movements—often oscillating more than five times a second. They most frequently affect the hands and head but can also strike other parts of the body and the voice; they usually worsen with time.

For Aldrich, the trembling progressed to her left hand after about five years. Within a decade it had advanced to her head. Her symptoms eventually shook her self-esteem, too. "The tremor made me feel old," she says. Although the disorder is sometimes called benign essential tremor, for many patients it is anything but benign: the vast majority, about 85 percent, say the tremor causes a significant change in their life. About one in four, according to a 1994 study by neurologists at what is now the University College London Institute of Neurology, have to change jobs or take early retirement. More than half of the people afflicted cannot find work, and one in three report withdrawing from social life.

Unfortunately, drug treatment fails to satisfactorily control essential tremor in up to 50 percent of all patients. Like many sufferers, Aldrich sought relief from several medications, including propranolol—more commonly used to treat high blood pressure and anxiety—and primidone, a first-line therapy for essential tremor that is also prescribed as an antiseizure medicine. The former helped for only a little while, and the latter involved side effects that Aldrich found intolerable, such as lethargy.

Then, in 2013, Aldrich saw a news program on television about an experimental new tremor treatment called focused ultrasound, or FUS, that used sound waves to destroy the malfunctioning nerve cells responsible for her condition. The report said that results from early clinical trials at the University of Virginia were promising. So Aldrich went online and signed up to participate in a future study.



Drawing a spiral like the one above (*a*) is a struggle for individuals with essential tremor, whose shaky hand will typically produce a disorderly jumble (*b*).

In recent years growing numbers of researchers around the world have begun experimenting with focused ultrasound. The accumulating evidence suggests that the technology could soon make painless, bloodless brain surgery a reality and revolutionize how many conditions are treated. Patients with cancers and movement disorders might avoid invasive procedures, radiation and lengthy hospital stays and instead be treated with relatively low risk, incision-free sonic surgeries. Focused ultrasound has been approved in Europe for treating es-

FAST FACTS

AN ULTRASONIC SOLUTION

1. **An experimental surgical technique, focused ultrasound (FUS), uses beams of sound to temporarily shut down or destroy brain areas.**
2. **Results thus far suggest that FUS can be especially effective in targeting structures below the cortex, such as those associated with movement disorders.**
3. **Researchers are also investigating the use of ultrasonic beams in opening up the blood-brain barrier and assisting clot-busting medications.**

FROM "ESSENTIAL TREMOR: EMERGING VIEWS OF A COMMON DISORDER," BY JULIÁN BENITO-LEÓN AND ELAN D. LOUIS, IN *NATURE CLINICAL PRACTICE NEUROLOGY*, VOL. 2, NO. 12; DECEMBER 2006

sential tremor, tremor caused by Parkinson's disease, and neuropathic pain. In the U.S., the use of FUS in brain surgery is still confined to clinical trials. Our institution is one of several participating in the first pivotal trial of focused ultrasound for essential tremor; we expect to release results in 2016. For people such as Aldrich, who are not helped by medication and have had no good surgical options available to them, the promise is enormous.

Since the early 20th century, people have used ultrasonic waves to "see." At high energy levels, however, sound waves can generate enough heat to temporarily disable cells. At even higher temperatures, the tissue is essentially cooked.

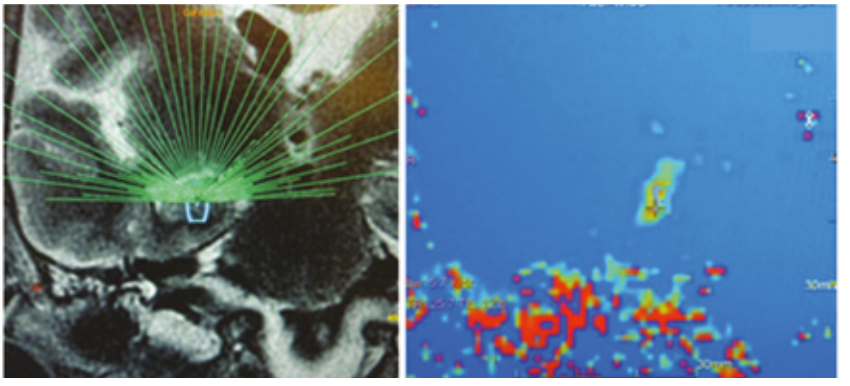
Making Waves

Vibrations in the air create nearly all the sounds that we hear. When a guitarist plucks a string, for example, its rapid back-and-forth movement is transmitted to the surrounding air molecules, which then relay the vibrations to more neighboring molecules, and so on. This creates a mechanical wave of compression and decompression that ripples through the air. When those sound waves reach our ears, their mechanical energy vibrates the thin membrane of our eardrums at the same frequency as the guitar string, which our brain interprets as a musical note. With standard tuning, the low E string of a guitar vibrates back and forth about 82 times a second, or, in scientific notation, at 82 hertz. The lowest sound most of us can hear is about 20 Hz; the highest is about 20,000. Any sound above what we can hear is, by definition, ultrasound.

Since the early 20th century, people have used ultrasonic waves to "see." As sound travels through the body, some of its energy bounces back from the tissues it encounters. Imaging devices, such as those used for diagnostic ultrasounds, use these echoes to create pictures in the same way that sonar uses reflected sound waves to map the watery depths. But sound waves also transmit energy to the tissues they traverse. Typically ultrasound conveys so little energy that it does no harm. Indeed, it is routinely used to image unborn fetuses.

At higher energy levels, however, sound waves can generate enough heat to temporarily disable cells. At even higher temperatures the tissue is essentially cooked. And at high acoustic intensity, ultrasound can prompt a powerful effect known as inertial cavitation. When ultrasound waves interact with dissolved gases in tissue fluids, they produce tiny bubbles that oscillate back and forth and increase the kinetic energy transmitted to the surrounding tissues. As these bubbles begin to collapse, inertial cavitation sets off shock waves that can damage and even liquefy the adjacent cells.

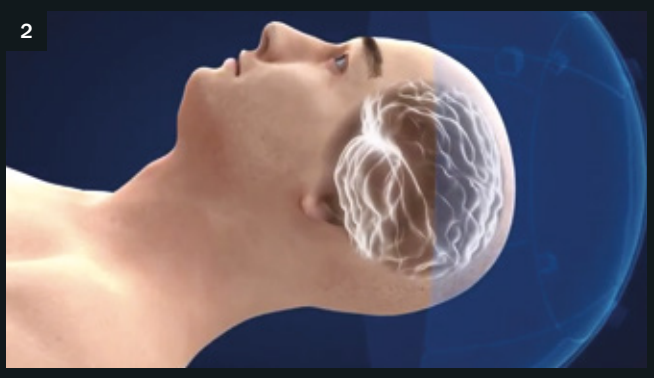
To generate enough energy and heat demands more than a single ultrasound beam. So-called focused ultrasound works by concentrating the power of hundreds of ultrasound beams on a single spot. The result is a unique surgical tool. In pioneering work conducted during the 1950s and 1960s, William Fry, a physicist at what is now the University of Illinois at Urbana-Champaign, working with neurosurgeon Russell Meyers, then at the State University of Iowa, treated Parkinson's patients using focused ultrasound to disable the substantia nigra and ansa lenticularis, two structures deep in the brain that malfunction in that disease. Until quite recently, though, such sonic brain surgeries had major drawbacks.

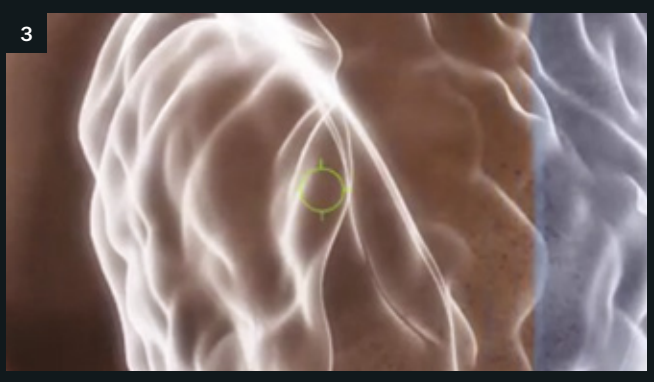


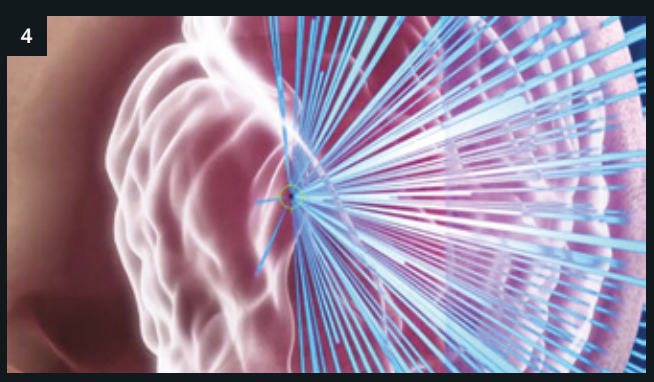
Before treatment, doctors use special software to plan where ultrasound beams should focus in the brain (*left*). During the procedure, MRI allows surgeons to track heat in the targeted area (*indicated by warm colors at right*).

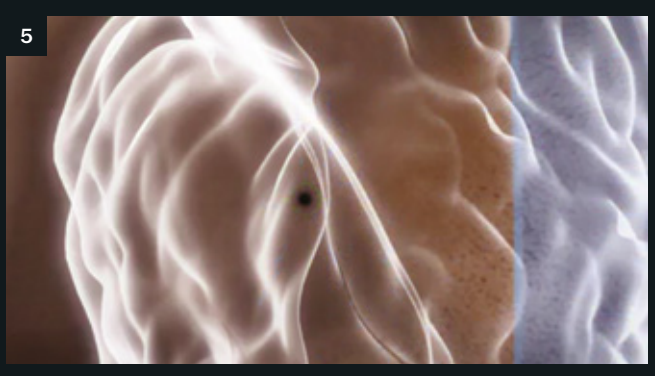
The skull presented the biggest challenge because sound does not traverse bone well. In fact, energy from ultrasound passing through the skull can be absorbed and converted to heat and can cause burns. In addition, the curving, irregular shape of the skull tends to bend, or diffract, the individual ultrasound beams, just as rippled glass will distort an image. This diffraction makes it difficult to fo-

FROM "POTENTIAL INTRACRANIAL APPLICATIONS OF MAGNETIC RESONANCE–GUIDED FOCUSED ULTRASOUND SURGERY: A REVIEW," BY STEPHEN MONTEITH ET AL., IN *JOURNAL OF NEUROSURGERY*, VOL. 118, NO. 2; FEBRUARY 2013









HOW IT WORKS

At the Swedish Medical Center, based in Seattle, we use a device called the ExAblate Neuro, developed by INSIGHTEC, an Israeli company that is also supporting our research with this technology. The device integrates a phased array of focused ultrasound beams and an MRI scanner so that they work as a unit.

Before treatment, a patient undergoes a CT scan to detail the shape, thickness and density of his or her skull, factors that determine how well the sound waves will traverse the bone. This information is then fed into a computer, which uses the data to adjust the output of the phased array so that it corrects for the skull's diffraction of individual beams, and they all emerge from the bone focused on the same target.

At the beginning of the procedure, we place a special metal frame on the patient's head to prevent any movement. Then the patient lies down and slips into a helmet containing transducers that convey the ultrasonic beams (*1*). This helmet also features a dome-shaped silicon diaphragm, which rests on the scalp. Cold water circulating through the diaphragm has two functions: it makes it possible for the sound waves to travel from the transducers into the head, and it prevents the scalp from being burned by the heat created as the ultrasound passes through the skull.

Once the patient is inside the MRI scanner (*2*), a radiologist or surgeon focuses the transducers on the target (*3*). To begin, low-energy sound beams warm the brain area in the crosshairs—a temperature change that shows up on the MRI scan. If the wrong spot "lights up" under these test beams, the device's focus can be adjusted in submillimeter increments. Once the correct positioning is confirmed, the higher-intensity therapeutic ultrasound beams start to fire (*4*) until the targeted tissue reaches about 60 degrees Celsius (140 degrees Fahrenheit)—at which point it coagulates (*5*). The neuroradiologist then retargets the array to the next area to be treated, and the process repeats. To destroy a pea-sized ventral intermediate nucleus (VIM) of the thalamus to treat essential tremor requires six to 20 cycles of high-intensity firing, which can take about five hours to complete.

Because the brain feels no pain, a patient can be awake throughout this procedure. This makes it possible to see if the treatment is having the desired effect. For example, a patient with essential tremor will see his or her tremor lessen as the procedure progresses. It also makes it possible to see if the treatment may be causing any unwanted side effects. If, for instance, during treatment, the sound waves inadvertently start to heat nearby sensory centers, the patient may report numbing in the face. Neurosurgeons can then switch off the ultrasonic beams, recalibrate and retarget before causing any permanent harm. *—S.J.M., R.G. and D.W.N*

COURTESY OF INSIGHTEC LTD.

cus the sound beams and reduces the energy they can impart. As a result, early ultrasound treatments of brain disorders required that surgeons first remove part of the skull—a procedure called a craniotomy—to make a window through which the sound waves could pass. These early procedures took up to 14 hours, with no guarantee that the sound waves were reaching the right location. Thus, although researchers made considerable progress using ultrasound to treat targets that were not encased in bone—benign breast tumors, uterine fibroids and enlarged prostates—similar treatments for brain conditions lagged behind.

Then, in the 1990s, scientists made two major advances. First, several research groups, including a team at General Electric then under the leadership of engineer S. Morry Blumenfeld, began to couple focused ultrasound with MRI so that they could be used in concert to direct the beams more effectively. Second, biomedical physicist Kullervo Hynynen and the late neuroradiologist Ferenc A. Jolesz, both then at Brigham and Women's Hospital in Boston, developed phased-array systems, which in essence made it possible to coordinate the timing, or phase, of the sound waves to correct the diffraction caused by the skull's irregular shape, thus removing the need for a craniotomy.

The result was a device of extraordinary power, allowing its operators to focus ultrasound beams with great precision and then watch how the beams altered the target tissue in real time. Because the coordinated MRI images can reveal temperature changes in real time, it is possible to use harmless, low-intensity ultrasound emissions to warm the tissue first and see exactly where the ultrasound beam is focused. Surgeons can then adjust the array—making corrections smaller than a millimeter, if necessary—before firing, dramatically reducing the risk of any accidental damage [*see box on opposite page*]. They can also use low-intensity ultrasound to briefly stun areas of the brain and test that they are not inadvertently targeting regions involved in important functions, such as speech. And because the brain feels no pain, the focused ultrasound procedure is completely painless, aside from some mild discomfort from the frame that holds the head in place.

Treating Tremor

Traditionally surgeons have most easily plied their craft on areas close to the brain's outer layer, or cortex. Structures deep within the brain—including those implicated in essential tremor, Parkinson's and some neuropathic pain disorders—have posed a much greater challenge. Focused ultrasound, however, actually works best on these hard-to-reach spots. Closer to the cortex, the ultrasound beams must travel at a shallower angle, causing them to have to travel through more of the skull and making them more likely to miss their mark.

Structures deep within the brain—including those implicated in Parkinson's and some types of pain disorders—are very difficult to access with conventional surgery. Focused ultrasound actually works best on these hard-to-reach spots.

To remedy essential tremor, most treatments seek to destroy or disable one of the brain's two ventral intermediate nuclei (VIM). These pea-sized clusters of neurons, located within the thalamus, near the very center of the brain, manage information about the position of our limbs in space, playing a vital role in the coordination and planning of movement. In essential tremor, the transmission of this information becomes garbled. And as the brain constantly tries to adjust and overcorrect that garbled information, it creates an oscillatory effect—which manifests as the condition's characteristic trembling. Removing the VIM, a procedure called a thalamotomy, can significantly reduce the tremors, but it can also cause serious side effects—including speech and balance problems, confusion and paralysis.

To minimize the risk, surgeons attempt to silence the faulty communication in only one of the VIM—usually the circuit that controls movement in the dominant hand or the side that is most seriously affected. Currently there are several ways to proceed. They can slip a catheter into the brain and, when the tip reaches a VIM, heat it to destroy the tissue. They can damage a VIM with high-energy radiation beams. Or they can use deep-brain stimulation, placing an electrode in the target VIM to deliver a low-voltage current that disrupts the nerve signals there. All three approaches can alleviate tremors, but drilling into the skull to place catheters and electrodes poses a

THE AUTHORS

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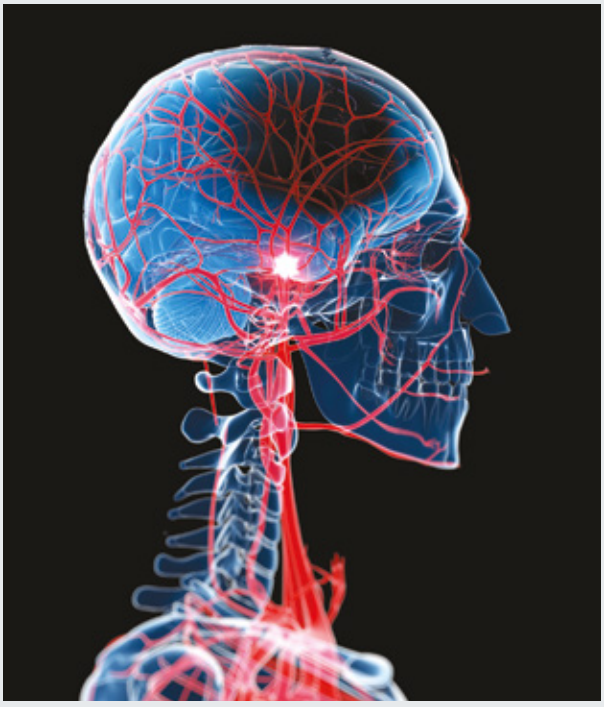

After a stroke, shown as a bright white area in this computer rendering, doctors must act quickly to prevent brain damage. New studies suggest FUS can enhance clot-busting treatment.

An Ultrasonic Solution for **Stroke**

Researchers have discovered that ultrasound can shake up fluids in a way that may limit the damage done by stroke. During so-called ischemic strokes, clots block the blood supply to parts of the brain, starving the tissue of oxygen until the neurons there die. But ultrasonic beams can accelerate the effects of a clot-dissolving drug, called tissue plasminogen activator (tPA), typically used to treat ischemic stroke. The sound waves stir up the blood clots, which have a jelly-like consistency, helping the medication to penetrate and dissolve them faster. Small clinical trials suggest that this approach may enhance the effects of tPA and improve outcomes. Larger clinical trials are under way to further study the technique's safety and efficacy.

Researchers at many centers around the world, including our own, are testing a new ultrasound device that resembles a headband and can be put on the patient's head in the emergency room so that treatment can start almost immediately. Another form of ultrasound treatment, using a catheter inserted in a blood clot in the brain, might also help stem the damage after hemorrhagic strokes, which occur when a blood vessel bursts and bleeds into the brain, forming large clots that often compress vital structures. In a 2011 study at our institution, one of us (Newell) and his colleagues found that ultrasound in combination with tPA can speed up the dissolution of clots in patients with hemorrhagic stroke and cut the time it takes to drain most of the fluid from these clots to about one day versus several days without the ultrasound. *—S.J.M., R.G. and D.W.N.*

risk of bleeding and infection. High doses of radiation can kill or damage healthy tissues.

In contrast, focused ultrasound requires no surgery or radiation and can pinpoint brain areas smaller than a grain of rice. In a pilot study published in 2013, neurosurgeon W. Jeffrey Elias of the University of Virginia and his colleagues, including one of us (Monteith), put focused ultrasound for thalamotomy to the test. In the study, which involved 15 patients with essential tremor, they found that it could destroy a VIM and decrease tremor and disability just as well as any existing method but with none of the associated risks.

A New Surgical Era

Beyond tremor treatments, neurosurgeons around the world are testing focused ultrasound in a range of incision-free brain operations. Promising applications abound. This technology could be used to destroy or alter brain areas associated with epilepsy, Parkinson's and pain conditions, shutting down problematic neural circuitry without harming neighboring cells. It might even be applied to neuropsychiatric diseases. In South Korea, clinical trials are under way to test the use of focused ultrasound to quiet a part of the prefrontal cortex thought to be overactive in depression and to shut down other deep-brain regions involved in obsessive-compulsive disorder.

Focused ultrasound shows particular potential for cancer treatment. In 2014 Monteith, working with his colleagues at the Swedish Neuroscience Institute in Seattle, performed the first surgery using focused ultrasound to treat a metastatic brain tumor—that is, a tumor that appears in the brain after cancer cells have spread from elsewhere in the body. And in the same year, a team led by neurosurgeon Javier Fandino of Cantonal Hospital Aarau in Switzerland and neuroradiologist Ernst Martin of University Children's Hospital Zurich demonstrated that they could use focused ultrasound to partially destroy a glioblastoma, a common and particularly deadly brain cancer.

The technology might also give pharmaceutical treatments a boost [*see box above*]. Many drugs cannot enter the brain because of the blood-brain barrier—in essence, a wall of cells that line the blood vessels within the brain. These cells,

GETTY IMAGES

called endothelial cells, form tight junctions with one another and filter out what cannot pass in between them. In general, they block large molecules that dissolve easily in water—including many important anticancer drugs, therapeutic proteins and antibodies. But research shows that focused ultrasound can temporarily pry the endothelial cells apart without destroying them, creating openings wide enough for bigger molecules to enter the brain. Researchers in Canada are now evaluating using this approach to treat Alzheimer's disease in preclinical studies. By briefly suspending the blood-brain barrier, focused ultrasound may give antibodies greater opportunity to attack the plaques involved in the disease.

Other scientists are hopeful that this trick may similarly increase the efficacy of some chemotherapies. Significantly, focused ultrasound disrupts the blood-brain barrier only in a specific location—namely wherever a surgeon directs the sonic beams. Thus, it is possible to apply a drug to a particular spot—say, a malignant growth—and spare the rest of the brain from any toxic side effects. Animal studies by neuroscientist Nathan J. McDannold of Brigham and Women's and others have demonstrated that focused ultrasound can disrupt the blood-brain barrier to allow therapeutic doses of a chemotherapy drug, doxorubicin, to enter the brain, suggesting such an approach could be effective in treating glioblastomas and other brain cancers in humans.

Relief at Last

When Aldrich first came to the Swedish Neuroscience Institute, she was enrolled in a randomized clinical trial. So she knew that she might be assigned to the control group, meaning she would undergo a fake procedure in which the team would do everything involved in a real treatment except administer the ultrasound. As it turned out, she was indeed in the control group. "I knew it was a sham," Aldrich says. "During the procedure, they would ask me to draw a spiral with pen and paper within a guided diagram. That's really hard if you have a tremor, and my spirals were not getting any better." After the trial study concluded, though, the hospital invited volunteers from the control group to undergo the real treatment, and so Aldrich returned.

In her case, the surgeons targeted the VIM involved in controlling movement in her dominant (right) hand. "I could hear the MRI machine and hear the water circulating through the cap device I wore, and I had expected I would feel some heat, but I didn't feel anything going on inside my head," she remembers. "But with each shot, my spirals got better. And they got better and better, and I thought, 'Hallelujah! I'm cured!'" Today Aldrich continues to have tremors in her head and left hand but none in her right hand. "I can write," she says. "I can pour coffee. I can do everything with that hand again." Not every patient responds as well as Aldrich did, but successful treatments often at least significantly reduce tremors. Sometimes the tremors recur, but they are usually less severe and less disabling when they do.

The technology could be used to destroy or alter brain areas associated with epilepsy, Parkinson's and pain conditions, shutting down problematic neural circuitry. It might even be applied to neuropsychiatric diseases such as depression.

Despite such encouraging results, for the moment focused ultrasound for treating brain disorders remains experimental. But this technology could radically change how we treat a wide range of ailments relatively soon. It is part of an emerging arsenal of surgical tools, including beam therapies that can demolish tumors with subatomic particles. If their promise is borne out, neurosurgeons will increasingly set aside their scalpels and drills and routinely perform painless, bloodless, incision-free operations. The term "revolutionary" is often overused to describe new innovations, but it is hard to find another term that better describes how focused ultrasound is likely to change the field of brain surgery. Just ask people like Carol Aldrich. M

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WHEN COPS LOSE CONTROL

The psychological drivers compelling police officers to wrongly use force are fairly clear. Finding ways to fix them is the challenge

By Rachel Nuwer

ILLUSTRATIONS BY FRANK STOCKTON

Trayvon Martin, Eric Garner, Michael Brown, Akai Gurley, Tamir Rice, Walter Scott, Freddie Gray, Samuel DuBose—the list of high-profile killings by police in the U.S. continues to grow. When this story went to press in September, officers had already shot and killed 680 people in 2015, according to a database maintained by the *Washington Post*. By its count, only 6 percent of the white suspects were unarmed, compared with 14 percent of the black victims. If the numbers reflected U.S. demographics, unarmed white deaths should be twice as high—and unarmed black deaths should be three times lower.

That African-Americans bear the brunt of unjustified police violence is not news: data from the U.S. Centers for Disease Control and Prevention, the Department of Justice and other sources indicate that blacks are three times more likely to be killed by police than whites are. But in recent months the visibility of the issue has surged. Highly publicized protests in Ferguson, Mo., and elsewhere; damning smartphone footage shared far and wide via social media; and movements such as Black Lives Matter have ignited a call for serious reform.

The outcry and demand for change now stem from citizens and police forces alike. Before determining how best to curb police violence against unarmed black citizens, though, many law-enforcement experts and scientists are trying to understand the psychological origins of the problem. Research is yielding some clues about how bias, fear and a lack of sleep, among other factors, can give rise to deadly split-second errors in judgment and action.

The larger challenge will be figuring out how to harness these insights to create evidence-based training programs that can prepare officers to cope justly with the unpredictable and life-threatening circumstances that are intrinsic to

the job. The fact is that the exact relation between police violence and racial bias remains an active and unsettled area of investigation. And not all the answers are in on whether training designed to reduce bias will be effective or if other approaches might offer greater benefits. But propelled by the current crisis, social psychologists, criminologists and neuroscientists are working on a range of remedies.

Bias in the Brain

Modern society looks down on overt expressions of bigotry, but evidence from both the real world and the laboratory betrays a darker truth: even as racial discrimination has lessened, racial inequalities have not. Blacks in America continue to face higher levels of poverty, incarceration and unemployment, among a myriad of other inequities. "Prejudice and bigotry are in retreat," says social psychologist Phillip Atiba Goff, currently a visiting scholar at Harvard University. "But I think we're a long way from having anything to celebrate."

For decades researchers such as Goff have sought to explain the ongoing racial divide, tracing it in part to something called implicit bias. This form of bias is so subtle that scientists find it even among people who appear to harbor no obvious prejudices. Unlike blatant racism, implicit bias is not an individually held belief but is one generally shared by everyone in a society. Because our brain naturally makes sense of the world by grouping things into categories, we all generate unconscious stereotypes based on the generalizations we absorb through experiences that include movies, television, music and the news.

With time and reflection, most people can mentally correct for implicit biases. "If I'm asking you to take a long, hard look at a job candidate, your implicit biases are not in play," Goff says. But in highly stressful situations, he adds, they can govern our actions. "If I get your heart rate up, get your adrenaline pumping, and say, 'If you don't make the right decision immediately, there will be consequences for you and your family,' then you may end up relying on implicit biases." In other words, implicit biases come into play precisely in the kinds of situations that lead to police shootings of unarmed suspects.

Beginning in the early 2000s, social psychologist Joshua Correll of the University of Colorado Boulder and his colleagues began a series of experiments in which they asked people to play a fast-paced video game that involved opponents facing off with various armed and unarmed suspects appearing on the screen. "Technically, skin color is irrelevant in this simple task, which is to shoot the guys with guns and not the guys without guns," Correll explains. "But what we find is that black targets, which society stereotypically associates with threat or danger, are more likely to lead to a shooting response."

In video game studies, both blacks and whites are more likely to fire at an unarmed black figure than a white one. And when the figures are armed, they shoot black targets faster.

Indeed, Correll has observed that his study subjects are more likely to mistakenly fire at an unarmed black avatar than at a white one. Similarly, they are faster to shoot at an armed black target than at an armed white one. And they are quicker to deem an unarmed white figure nonthreatening, compared with an unarmed black one. These patterns hold up whether a shooter is outwardly racist or not—and even when the shooter is black.

Kurt Hugenberg and Galen V. Bodenhausen, both then at Northwestern University, further discovered that the more implicit bias a white person harbors, the more likely he or she is to perceive a black face as hostile. Again, this reaction reflects implicit prejudice, so people are unaware of the perceptual skew. "This means we can't just say, 'Don't go shooting friendly black people,'" says David Amodio, a psychologist and neuroscientist at New York University. "Stereotyping is already causing a neutral black face to appear as more threatening."

Amodio and his colleagues have looked for what prompts some of these responses in the brain. In a series of experiments during the past decade, they have found that when white volunteers are presented with a black face, they appear to experience more fear than they do in response to a white face. Specifically when study participants look at black faces, they have stronger startle reflexes linked to activation in the amygdala, which is involved in emotional responses.

Our implicit biases can render black faces not only more threatening but less human, too. In 2008 Goff and his colleagues reported that people who had been subliminally "primed" by viewing photographs of black faces instead of white ones were faster to identify obscured, pixelated images of apes that slowly improved in visibility over time. The team also found that news articles written about black convicts are more likely to contain dehumanizing words (such as barbaric, beast, predator, stalk and savage) and that convicts portrayed as being more apelike have a greater chance of receiving a death sentence.

FAST FACTS

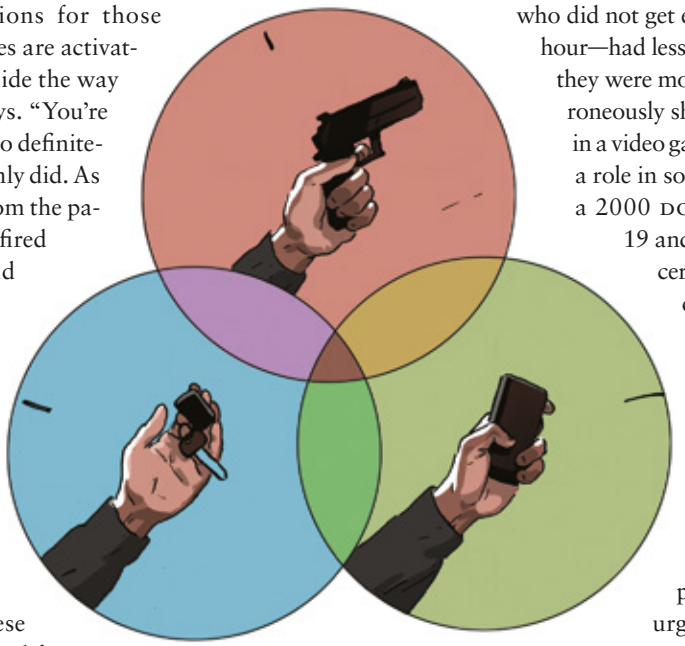
TARGETING POLICE VIOLENCE

1. As the list of unarmed black Americans wrongfully killed by the police continues to grow, citizens and police forces alike are demanding meaningful reform.
2. Research suggests that blacks bear the brunt of unjustified police violence in the U.S. in part because of implicit bias, an unconscious, society-wide form of prejudice.
3. Tackling implicit bias with training is one tactic being tested in the field, but training to help officers manage stress and defuse tense situations could prove more beneficial.

"If in the deep recesses of someone's mind, they perceive white people as being more human than black people, they'll respond to those groups differently," says social psychologist Jack Glaser of the University of California, Berkeley. "Combine that with bias to see a weapon, and those two things go a fairly long way to explain what we're seeing with use of deadly force."

"Man with Gun"

Last November, just five days before Thanksgiving, 12-year-old Tamir Rice was playing with a toy gun in a park in Cleveland. According to a call from a concerned citizen, he was pointing it at people. Two police officers, 26-year-old Timothy Loehmann and his partner, 46-year-old Frank Garmback, responded. As soon as the dispatcher radioed over key descriptors—black, male, gun (she did not mention that the caller described it as "probably fake")—they likely triggered subconscious impressions for those officers. "Once these stereotypes are activated in the mind, they start to guide the way we see a situation," Amodio says. "You're tuned to see a hostile person who definitely has a gun." Loehmann certainly did. As captured on tape, he jumped from the patrol car as it rolled to a stop and fired twice. The toy-wielding child died the next day.



These so-called threat-perception failures—mistaking a toy gun for a real one or a cell phone or some other object for a weapon—are not uncommon. An investigative report commissioned by the Department of Justice (DOJ) on the use of deadly force in Philadelphia found that these psychological blunders accounted for 49 percent of officer-involved shootings of unarmed citizens from 2007 to 2013. Both black and white officers were more likely to make errors when the suspect was black.

Goff and his colleagues have found similar misperceptions in the lab. They subliminally exposed both undergraduates and police officers to images of black and white faces and then asked them to identify mystery objects in deliberately blurred photographs. The subjects were faster to correctly label guns in the degraded images after "seeing" black faces. In reverse, they were also quicker to focus their visual attention on black faces after seeing split-second images of guns: the participants spotted a moving dot near a black face faster than they noticed one near a white face. "Thinking about black people makes people think about weapons, and thinking about weapons makes people think about blacks," Glaser says. "So officers, when confronted with a black person, are more prone to see a weapon." The fact that blacks are regarded as threatening, Goff points out, "is not endemic to the culture of policing exclusively—it's an American problem."

Goff notes that stereotype-driven intuition can readily cause a cascade of erroneous suspicion. When a cop walks toward a person he or she believes looks suspicious, that person may begin to seem even more uneasy—precisely because the police officer is approaching. As Goff points out: "Black folks get nervous when they're worried about being stereotyped as criminals." As the suspect becomes more uncomfortable, the officer's suspicions are reinforced. If the suspect tries to evade the situation, an altercation can ensue. "Implicit bias plays a role in every one of those steps," Goff says. "It greases the wheel of disaster in terms of interpersonal interactions."

Other emotions and circumstances can also lead to dangerous escalations. In a study published in 2013 in the journal *Basic and Applied Social Psychology,* Correll and his colleagues found that both undergraduates and police recruits who did not get enough sleep—even by just an hour—had less cognitive control. As a result, they were more likely to act on bias and erroneously shoot at unarmed black targets in a video game. Exhaustion may well play a role in some real-world shootings, too: a 2000 DOJ study found that between 19 and 41 percent of examined officers showed signs of severe sleep deprivation, depending on the test used to measure the deficit. In the test that found the former figure, the exhaustion caused slightly more than 6 percent of subjects to suffer impairments on par with being legally drunk.

In other situations, tempers suddenly flare out of an urge to exert power and dominance. Police can be readily caught up in a "good guy/bad guy" mind-set, charged, as they are, with maintaining law and order and keeping the peace. In an infamous 2014 incident in Staten Island, N.Y., Daniel Pantaleo, a 29-year-old officer, accidentally suffocated 43-year-old Eric Garner, an unarmed black man he suspected of illegally selling loose cigarettes, restraining the asthmatic Garner in a choke hold when he resisted officers' attempts to handcuff him. Patrick J. Lynch, president of the Patrolmen's Benevolent Association of the City of New York, was quick to offer an explanation that reflected this line-in-the-sand mentality. Too many people attempt to protest police decisions on the street, he said in a press conference, and "resisting arrest is a real and dangerous crime."

In yet other cases, impulsivity triggered by fear lays the groundwork for deadly force. This past summer 25-year-old officer Ray Tensing killed 43-year-old Samuel DuBose, another unarmed black man, during a routine traffic stop in Cincinnati. Tensing made a snap decision that DuBose would run him over

and panicked, shooting him in the head. "Clearly, that officer was incompetent and should never have been a policeman, but I don't think his intention was to kill anyone that day," Glaser says. "Police are human, and there will be variability in their maturity, self-control and courage in a situation like that" [see "Who Should Be a Cop?" on page 50].

Can Better Training Help?

Some studies hint that it may be possible to reduce implicit bias through exposure. In 2005 Ashby Plant, a social psychologist at Florida State University, and her colleagues described an experiment using a shooter video game similar to Correll's. They recruited 50 primarily white officers and found that the more they played the game—in which black and white "suspects" were equally likely to be unarmed—the more accurate and less biased they became in their targeting. In Correll's experiments, too, cops generally made better targeting decisions than undergraduates did—they were no more likely to shoot unarmed blacks than they were unarmed whites—but they were still faster to pull the trigger at black avatars than white ones when they did fire.

Whether such improvements through training can translate from the lab to the streets, Correll says, "is the $10,000 question." Other research also indicates that increasing the number of positive interactions with members of stereotyped groups might help blunt subconscious bias. Ken Paller, director of the cognitive neuroscience program at Northwestern, and his colleagues have demonstrated the potential merits of so-called counterstereotype training—seeing faces paired with words that run counter to cultural stereotypes, for instance. They are even investigating whether pairing sounds with these antistereotypes—and then playing those sounds when subjects sleep after the training—might concentrate their effects.

But no matter how promising any of these results may seem, "the real world is not a safe, controlled little video game with pictures popping up on a screen," Correll says. "In the real world, it's chaotic and messy, and you're scared for your life." Plant adds: "We don't want to make large generalizations about things we see in undergraduates in the lab and then suggest that the New York City Police Department do that."

Although statistics on cop shootings of unarmed blacks suggest that implicit bias plays a key role, Correll points out that the association, no matter how compelling, is only correlational. Are officers really homing in on race, or is skin color confounding the actual variable (or variables) driving the disparity? "We know that a black person is much more likely per capita to die at the hands of an officer—just squint at a DOJ report, and that's painfully obvious," Correll says. "But in the exact same situation, if a white guy and a black guy are in the same neighborhood, wearing the same clothing and behaving in exactly the same fashion, would an officer treat them differently? That, we don't know."

In fact, no official national data exist on police behavior or officer-involved shootings. "They say you can't hide a body, but it turns out that criminal-justice-statistics folks miss a fair amount of homicides, partly because they categorize them as accidental deaths, and the Bureau of Justice Statistics does not track officer-involved shootings directly," Glaser says. "There's no one clearinghouse for reliable data."

To amend that situation, Goff—with the support of Glaser and other researchers—has co-founded the Center for Policing Equity. The consortium will serve as the first national justice database and collect information about pedestrian stops, complaints filed against officers, and those officers' discipline records and their use of force. So far departments responsible for policing more than one third of the U.S. by population have agreed to participate.

"The first goal is just to figure out how often this stuff hap-

THE AUTHOR

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CASE STUDY

Camden, N.J.

In a crime-battered city, new training aims to reshape the relationship between police and community

Just a few years ago Camden was caught in a cycle of perpetual violence. So New Jersey's seventh-largest city (current population: 77,332) took a radical step: in 2011 it fired 163 officers, approximately half of its police force. The next year proved especially deadly, with one person shot every 32 hours. But Mayor Dana Redd had a plan. She disbanded the rest of the department to make way for a new countywide force and hired John Timoney, a former Miami police chief, and police consultant Joe Cordero and asked them to design strategies that could develop stronger inroads with the local community.

On May 1, 2013, Scott Thomson, who was previously running the city's squad, was sworn in as chief of the all-new Camden County Police Department. "I knew we had only one opportunity in getting it right to establish the type of culture we needed to make Camden a safer, more vibrant, prosperous place," he says. From the start, Thomson implemented more community policing and new education workshops. Camden will be the only force in the country to have all 372 of its officers trained as "ethical protectors," a version of a program used to teach marines about the responsible use of force and community building.

Former marine Jack E. Hoban, who developed the law-enforcement program, is teaching the first class of Camden officers, who will then mentor the rest of the force. "Police may have to take a life in order to save a life," he notes, "and so there needs to be an extra level of skills and training." Police officers need to have strong ethics and verbal conflict-resolution skills and to learn how to balance policing and home life to manage stress levels.

Researcher Steven Olson and his team at Georgia State University plan to evaluate the impact of the program once more officers have been trained. But reducing stress should help officers better control impulsivity and implicit bias—both of which can contribute to violence. In a 2011 study, researcher Michael L. Arter of Pennsylvania State University studied 32 officers from two Southern metropolitan police forces and found a correlation between higher levels of stress and reported acts of deviance—including heavy drinking, promiscuity and dishonesty—both on the job and off. When the stress was off, mostly from reassigning positions, these officers stopped acting out.

The program also jibes with one of the newest ideas promoted in policing circles, called procedural justice: when residents are treated fairly, they view the police more positively, and their interactions with them become safer. But procedural justice can be hard to implement. In a 2014 study, political scientist Wesley Skogan and his colleagues at Northwestern University evaluated the one-day training of 8,700 police officers, 230 new recruits and some civilian officers in Chicago. They found that many officers responded well to the instruction in the short term but became less supportive of some principles over time. The researchers conducted a survey of randomly selected officers to assess the long-term impact of training. Whereas some of the ideas of procedural justice endured, many officers still did not trust the public, which is imperative to create goodwill in a community. In Camden, "it will be reinforced on an ongoing basis so as to become the culture of our police department," says Lieutenant Kevin Lutz, chief instructor for the Camden County College Police Academy.

Also as part of that cultural shift, officers are walking beats more and attending weekend barbecues and potluck dinners. "The only way to truly build trust with another human being is through contact," Thomson says. "The walking beat creates the opportunity for officers to have interactions with the people that are separate and apart from a moment of crisis or interaction predicated on enforcement."

Like procedural justice, community policing gets mixed reviews. In a 2014 paper, Charlotte Gill of George Mason University and her colleagues analyzed 65 studies of community policing and concluded that, overall, such programs have positive effects on community satisfaction but do not deter crime. But "when the police build positive relationships with the community, they can impact proximal outcomes like citizen satisfaction and trust, which may set the scene for effective problem solving to occur," they wrote. This held true for Thomson and his staff. They engaged their network of community leaders to good effect this past July 4, when an officer shot and killed an unarmed Hispanic man. After frank discussion, police leaders released 911 tapes and put the officers involved on administrative leave; community leaders called for calm, and the public listened.

Whether Thomson's tactics will change crime rates in Camden over the long term remains to be seen, but so far the statistics are encouraging. Since he took charge, the force has fielded more than 4,500 calls about firearms, but officers have shot their guns only nine times, with one death. Moreover, the economy has improved, violent crime has dropped 30 percent and murders involving guns are down 50 percent. "We will never reach a finish line," Thomson says. "It's one that we will work toward every day, understanding that it's a perpetually fragile environment that we hold near and dear." —*Cara Tabachnick*

pens, how severe it is, under what conditions it happens and how racially disparate the treatments are," Goff says. "This database will allow us to begin—emphasis on begin—to make distinctions between law enforcement's responsibility for racial disparities in policing and the responsibility of the rest of us for creating a racially disparate criminal justice system."

If we currently lack basic understanding about policing and the role that implicit bias plays in it, we know even less about how to counter the problem. "We're still a long way off from understanding why, exactly, a controversial shooting incident might occur, much less knowing how to implement a large-scale intervention to prevent such things," Amodio says. "My guess is that any current proposals for reducing such incidents are, at the present time, based more on speculation and opinion than evidence."

Premature interventions, Correll warns, could cause more harm that good. In one telling study from 2001, Keith Payne, now at the University of North Carolina at Chapel Hill, and his

colleagues investigated how conscious goals can be used to control the unconscious influence of stereotypes. As expected, participants initially misidentified harmless objects as weapons more often after seeing an image of a black face; after seeing white faces, they were more likely to misidentify a weapon as a harmless object. But when the researchers admonished the participants to remain unbiased, their performance actually got worse. "It boomeranged," Correll says. "By trying not to think in racial terms, they have to think in racial terms, which leads to hypersensitivity to race and more bias."

By extension, training designed to neutralize officers' feelings about race could wind up unintentionally having the opposite effect, putting suspects in even graver danger. Conversely, if cops are taught to be overly self-conscious of their implicit biases, Correll says, their ability to accurately judge a situation could be compromised, putting their own lives at risk. And if legislators, mayors and police chiefs invest time and money in half-baked interventions that ultimately do not work, he adds, they may just throw up their hands and write off any future reform efforts.

Reality Check

While science incrementally chips away at these problems, police forces and the public are clamoring for immediate action. A number of training programs are currently being deployed [see "Camden, N.J.," on preceding page]. Lorie Fridell, a criminologist at the University of South Florida, says she and her colleagues are overwhelmed with requests from police departments, and they are trying to build a greater awareness of implicit bias. "Many in policing reject the allegations of widespread biased policing because they look at themselves and those around them, and they don't see any racists," she says.

There are no empirical evaluations of the new training programs in place, but a few have produced results anecdotally. Las Vegas, for example, hit an annual high of 25 officer-involved shootings in 2010. But after an aggressive reform program—including training in how to de-escalate confrontations and specialized courses on fair and impartial policing, the latter taught by Fridell and her colleagues—the stats improved dramatically. Through the end of August, Las Vegas officers had been involved in just nine shootings for the year to date.

Officers should have to meet proficiency requirements in conflict resolution and social skills, not just at the shooting range.

Some of that progress can probably be attributed to the lessons in managing tense situations. "Sometimes officers may be justified at the last split second in using deadly force," Fridell says, "but if you look at the earlier decisions they made, they put themselves in that situation." To that end, Dennis Rosenbaum, a professor of criminology, law and justice at the University of Illinois at Chicago and executive director of the National Police Research Platform, calls for more "emotional intelligence and social skills" so that officers can more adeptly deal with someone who is upset and recognize if the person poses a genuine threat. He thinks officers need active training in these areas: "When police officers go to the shooting range, they are required to hit the target *x* percent of the time to get certified. Where's the proficiency requirement for social skills and conflict de-escalation?"

Jonathan Wender, a sociologist at the University of Washington with more than 20 years of experience as a police officer and a sergeant, and Brian Lande, a sociologist who currently serves as a patrol officer in Richmond, Calif., are attempting to fill this gap. In 2010 the Defense Advanced Research Projects Agency offered them a $40-million budget to design an evidence-based training course for teaching military personnel how to handle people of

Who Should Be a Cop?

Recruitment presents an enormous challenge in modern policing. In hopes of finding those people best suited to the role—interested in helping citizens and not just locking them up—many forces administer psychological examinations during the hiring process. There are no clear guidelines, but some studies hint at traits to look for.

Paul Detrick of Florissant Psychological Services in Florissant, Mo., and John Chibnall of Saint Louis University reviewed personality test data from 288 would-be police officers in the Midwest. They found that applicants who scored low on measures of neuroticism and high on extraversion and conscientiousness later proved to be the most successful officers.

In a 2013 study, Peter Weiss, then at the University of Hartford, and his colleagues linked the performance reviews of 4,348 police officers to their scores on the Minnesota Multiphasic Personality Inventory, a test used by many departments to prescreen job candidates for psychological disorders. As one might expect, they found that those with high scores—and potentially more psychological issues—had more problems later on. High scorers were more likely to receive citizen complaints, to be terminated for cause and to engage in problematic weapon use, among other undesirable behaviors.

Higher education is also beneficial. Many departments require only a high school diploma, but a 2011 review in the *Journal of Criminal Justice Education* found that officers with college degrees were associated with fewer violent incidents. Similarly, a 2008 study showed that college-educated patrol officers were significantly less likely to be involved in shootings. —*C.T.*

different backgrounds in high-risk situations. Now their company, Polis Solutions, is providing similar coaching to local police forces across the country. Antibias training is part of their program, but it primarily focuses on practical ways to reduce negative interactions between the police and public.

"We think it's important to pull back from these high-level, abstract explorations about politics, culture and morality and instead look at the dynamics of interactions," Wender says. "We ask, 'What makes a good stranger? What enables people, especially when things are tense, to get things right?'" Using evidence from psychology, anthropology, linguistics and cognitive science and supported by the DOJ, the philosopher cops, as they call themselves, train officers to build empathy and trust, taking cues from someone's words, body language, facial expressions and other traits. Trainees currently practice with actors but may in the future have access to "social encounter" simulators. "Social interaction must be taught like any kind of skill," Wender says. "You can't teach someone to swim by telling them to read a book about it."

Their training also uses case studies. When 30-year-old state trooper Brian Encinia pulled over 28-year-old Sandra Bland in July for failing to signal a lane change in Waller County, Texas, she griped, and he responded with bullying, threatening to "light [her] up" with a Taser. He arrested Bland, who was later found dead in her jail cell. Wender says her death likely could have been avoided if Encinia had taken a different approach: asking Bland why she was upset and expressing some understanding of her frustration. "There are identifiable errors that he shouldn't have made and could have been taught not to make," Wender says. "These skills are eminently trainable, but they have to be delivered in a realistic and sustainable way that goes beyond just checking a box."

Better social skills may help officers avoid scenarios that typically lead to force, but it is impossible to eliminate high-stakes situations altogether. To prepare, Glaser suggests that officers practice in sessions that closely mimic real-world crises, preferably with black actors wielding something like a paintball gun. Some deputies shy away from this idea for fear of being accused of training cops to shoot black people. But without such training, Glaser says, officers will be less able to avoid that very scenario. "Anecdotally, I've heard from officers that once a gun is drawn or you think your life is in danger, you'd better hope you're well trained because you're no longer under control," he says. "Some say they've even soiled themselves—it's absolutely terrifying."

If Wender and others were to develop empirically tested, effective and long-lasting training programs, they would face one final problem: how to implement them. Unlike many other countries, the U.S. does not have a single police force but instead has 18,000 individual departments that operate on state, city or county levels. For this reason, issuing a federal decree that every department must undertake some specified reform program would not work, Fridell says. To try to address that challenge, in late August the organizers behind Black Lives Matter launched Campaign Zero, a series of policy-reform recommendations tailored to the federal, state and local level.

Their recommendations regarding training largely echo what social psychologists are promoting—teaching better social and coping skills and raising awareness about implicit bias. Aiming too broadly at reducing implicit bias, however, is a moving target: "The black-danger and black-bad associations are malleable," Correll says. "That means they can be reduced, but by the very same token, that also means they can come right back." The only way to ever rid ourselves of implicit biases is to fix the underlying societal inequalities that create them. "Concerning ourselves with eliminating implicit bias is chasing our tails," Goff emphasizes. "We should actually concern ourselves with eliminating inequality—the bias will follow." M

MORE TO EXPLORE

- *Washington Post*'s database of police killings in 2015: **www.washingtonpost.com/graphics/national/police-shootings**
- The Counted: *Guardian*'s database of people killed by police in the U.S.: **www.theguardian.com/us-news/ng-interactive/2015/jun/01/the-counted-police-killings-us-database**

From Our Archives

- **Outrageous.** Michael Shermer; Skeptic, *Scientific American*, July 2015.

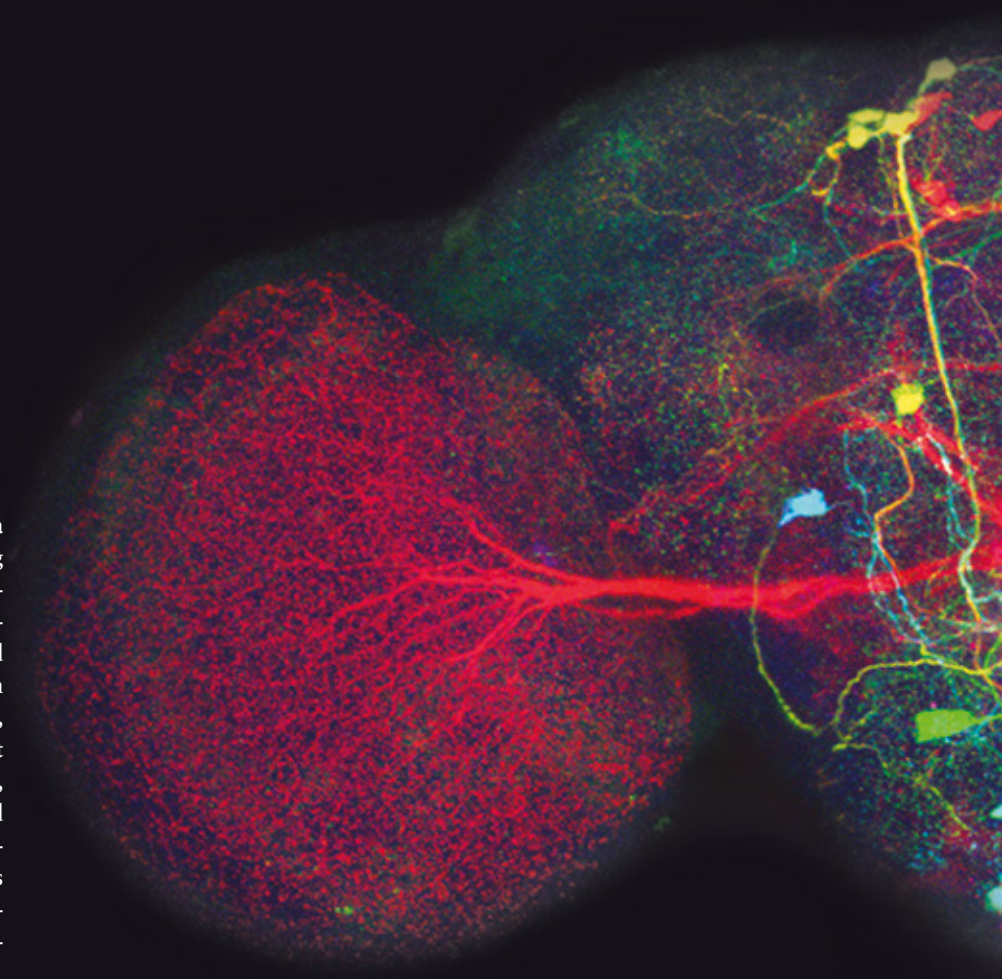
THE BRAINBOW CONNECTION

A colorful technique is shedding light on the function and development of neural circuits

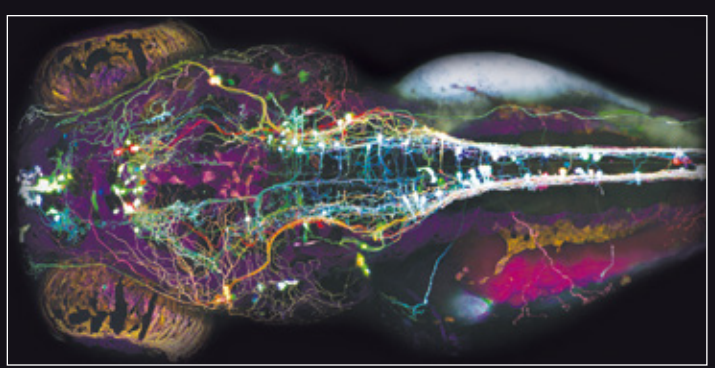
By Diana Kwon and Liz Tormes

Splashes of fuchsia, streaks of crimson and a smattering of taupe. When these dazzling displays of color—each hue denoting a different neuron—first appeared in the neuroscientific community in 2007, researchers hailed them as a novel way to understand brain structure. By inserting genes from bacteria, corals and jellyfish to code for three different fluorescent proteins into mouse nerve cells, Harvard University neuroscientists created neurons that would express a random combination of the proteins. These combinations could illuminate cells in up to 90 distinct colors, transforming scientific images into visually striking works of art.

Originally developed to map neural circuits, today some scientists believe that the technique, called brainbow, is far better suited to other tasks, such as offering a closer look at what specific neurons do and at the brain cells behind behaviors. And because the daughter cells of brainbow neurons inherit the same color as their parents, scientists can use this method to study how clusters of cells grow and develop. This collection of images gives us a glimpse into these recent discoveries. M



Private Lives of Flies
In the fruit fly brain shown above, scientists selectively labeled neurons that release octopamine, a neurochemical involved in several behaviors, including sleep and aggression.



THE AUTHORS

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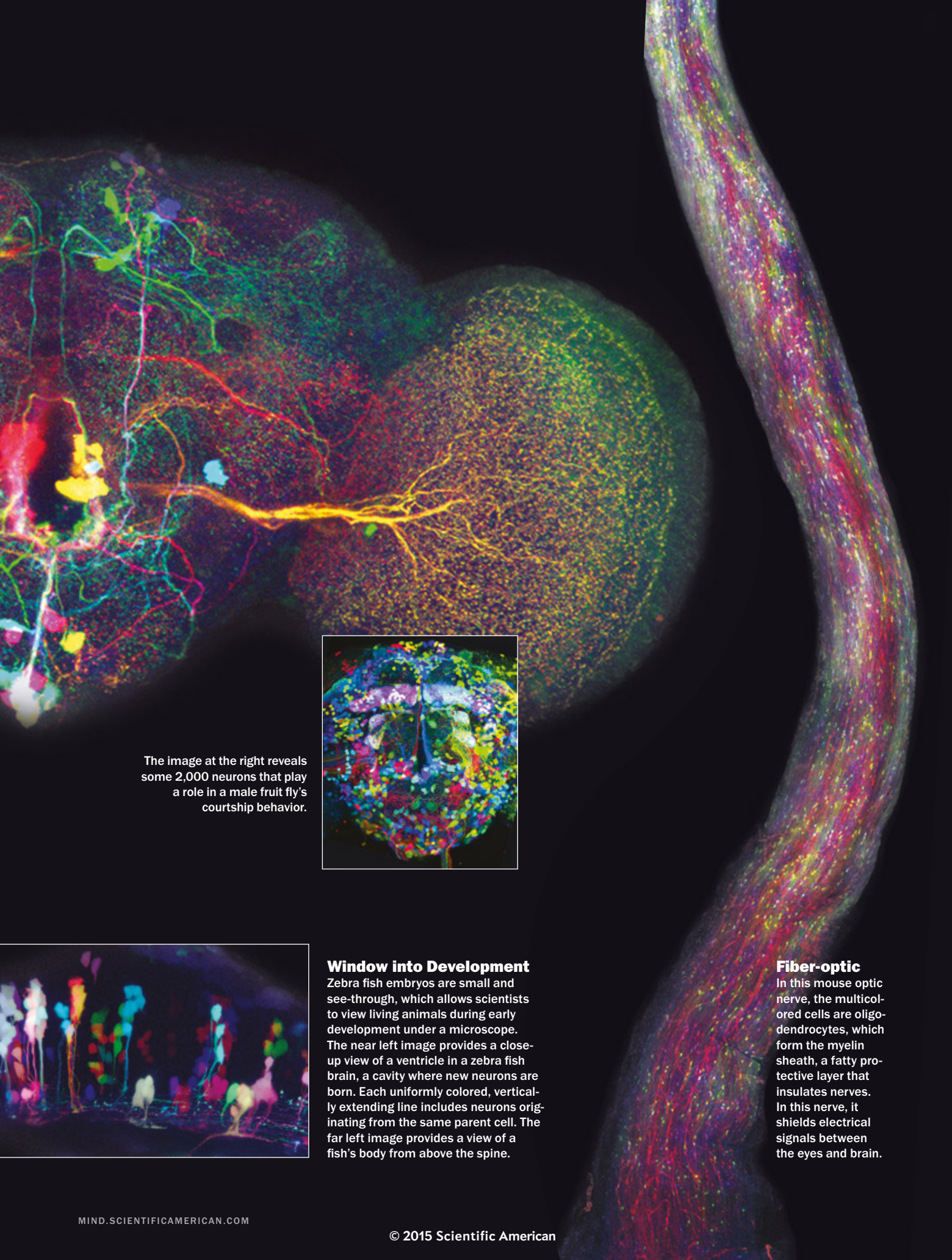
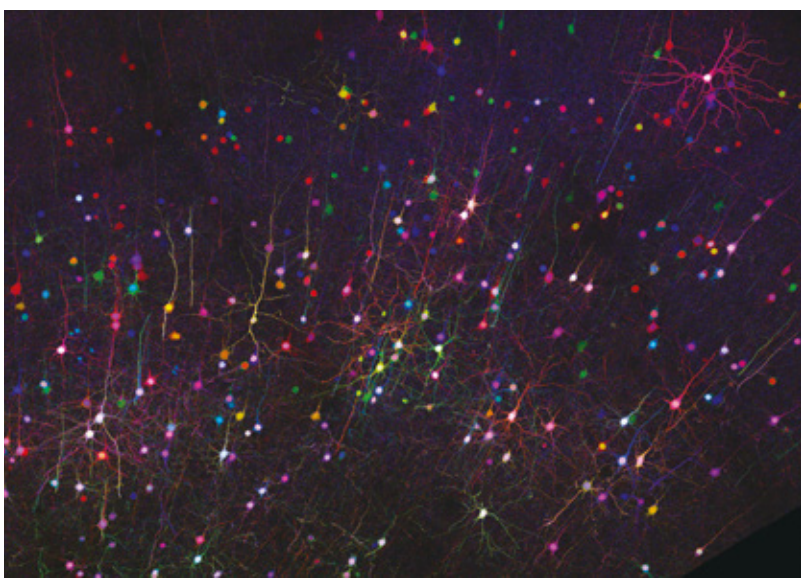


The image at the right reveals some 2,000 neurons that play a role in a male fruit fly's courtship behavior.

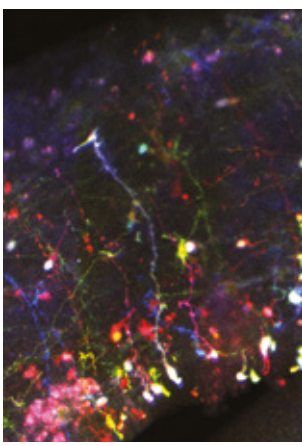
Window into Development
Zebra fish embryos are small and see-through, which allows scientists to view living animals during early development under a microscope. The near left image provides a close-up view of a ventricle in a zebra fish brain, a cavity where new neurons are born. Each uniformly colored, vertically extending line includes neurons originating from the same parent cell. The far left image provides a view of a fish's body from above the spine.

Fiber-optic
In this mouse optic nerve, the multicolored cells are oligodendrocytes, which form the myelin sheath, a fatty protective layer that insulates nerves. In this nerve, it shields electrical signals between the eyes and brain.

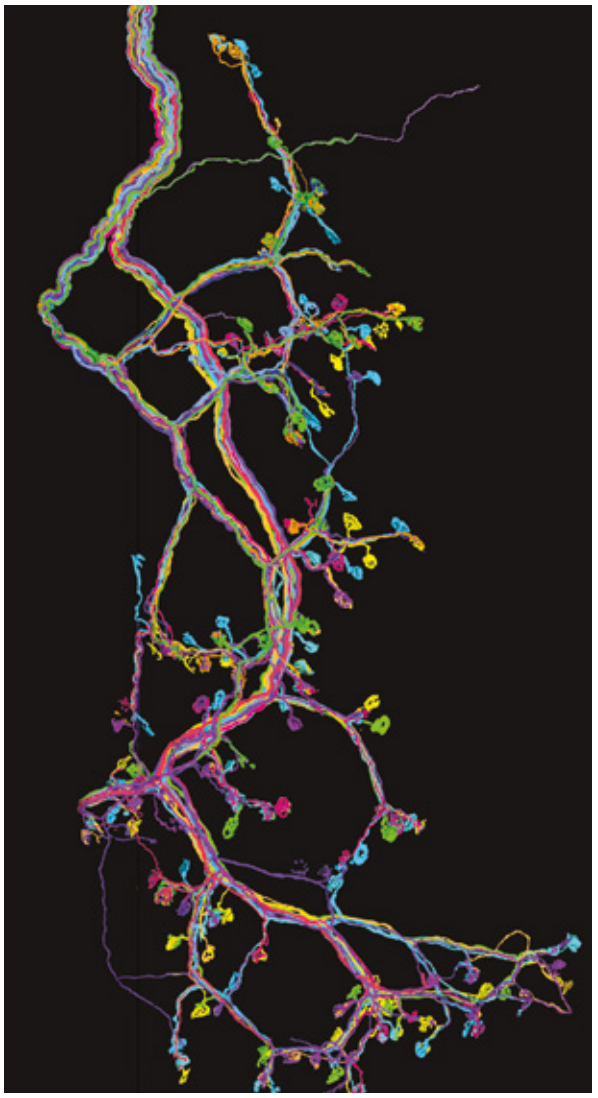
Original Brainbow Neurons
The image above, showing human embryonic kidney cells, was one of the first proof-of-concept demonstrations of brainbow, published in 2007.

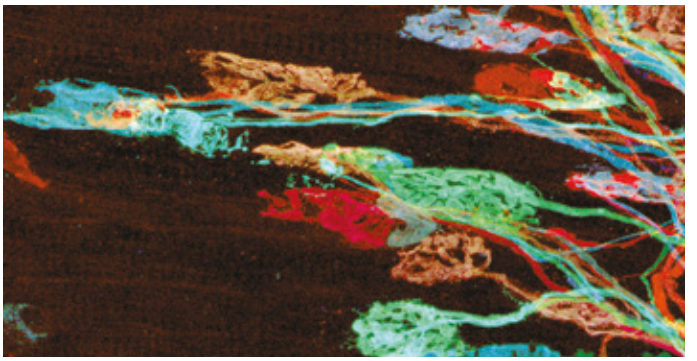


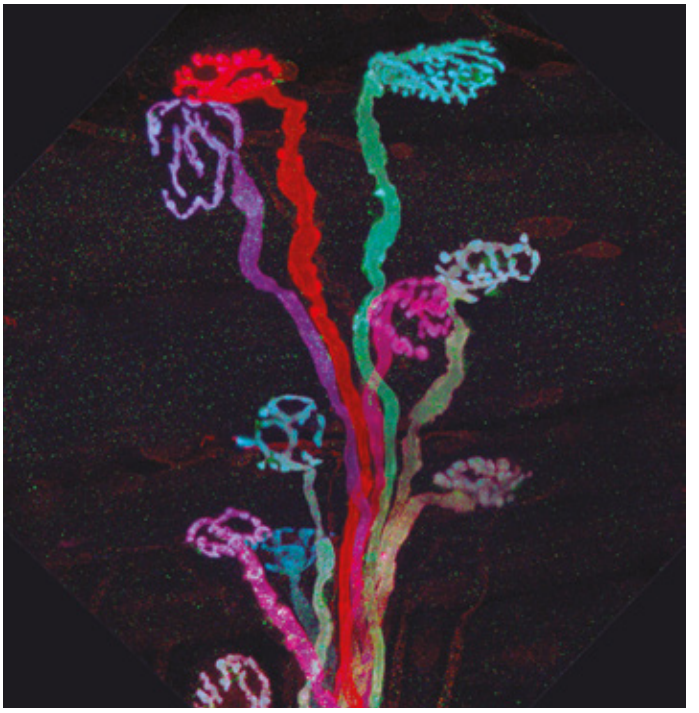
Starry Cortex
Multicolored pyramidal neurons illuminate a mouse cortex at the left. These neurons are among the most common type of cell in the mammalian brain and are believed to be involved in complex kinds of cognition.



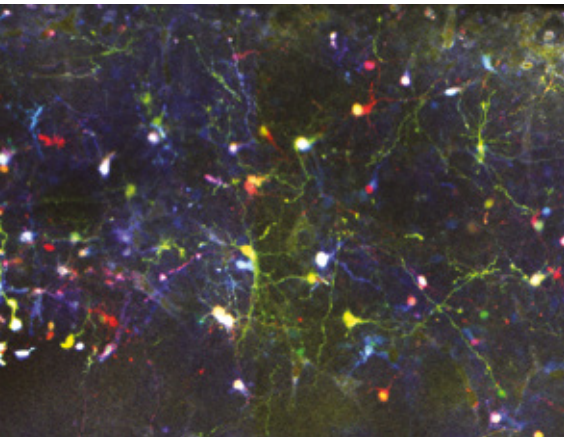
COURTESY OF PHUONG CHUNG AND JULIE H. SIMPSON (*fruit fly images*); ZACHARY TOBIAS, ZEBRA FISH VENTRICLE PHOTOGRAPHED AT TAMILY A. WEISSMAN'S LABORATORY AT LEWIS & CLARK COLLEGE OF ARTS & SCIENCES (*zebra fish neurons*); COURTESY OF ALBERT PAN *Medical College of Georgia, Georgia Regents University* (*zebra fish body*); COURTESY OF ALAIN CHÉDOTAL *Vision Institute, INSERM* (*mouse optic nerve*); FROM "TRANSGENIC STRATEGIES FOR COMBINATORIAL EXPRESSION OF FLUORESCENT PROTEINS IN THE NERVOUS SYSTEM," BY JEAN LIVET ET AL., IN *NATURE,* VOL. 450; NOVEMBER 1, 2007 (*kidney cells*); FROM "MULTIPLEX CELL AND LINEAGE TRACKING WITH COMBINATORIAL

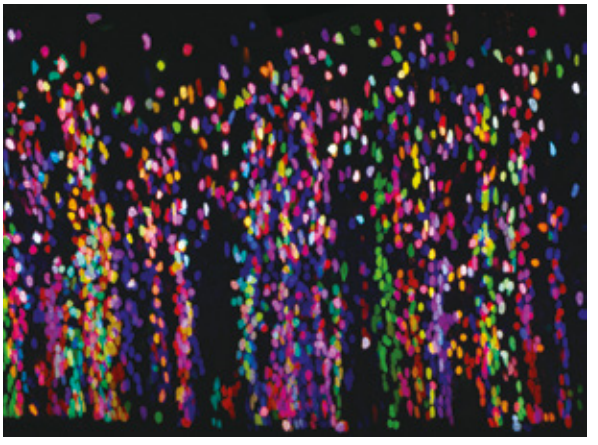






Giant Junctions
The limits of current technology make it hard to see the synaptic connections between neurons using brainbow. One exception is the neuromuscular junction—shown in mice in the two images at the right above—where the neurons that connect with muscle fibers are large and few in number. Each ribbon of color is a motor neuron that competes with its neighbors until only one remains at the synapse. Scientists can combine these images to construct a more complete view of a motor neuron circuit, as depicted in the left image.





Chicken or Egg?
Scientists also use brainbow-based techniques to study neural development in chicks. In the far left image, researchers labeled neurons in an area near the front of the developing brain of an 11-day-old chick embryo. The near left image depicts neurogenesis—or the growth of new neurons—in a chick's spinal cord. Daughter cells match the color of the parent cell.

LABELS," BY KARINE LOULIER ET AL., IN *NEURON,* VOL. 81, NO. 3; FEBRUARY 5, 2014 (SUPPLEMENTAL INFORMATION) (*mouse pyramidal neurons*); COURTESY OF IAN BOOTHBY AND JEFF W. LICHTMAN *Harvard University* (*mouse neuromuscular junction* and *motor circuit images*); FROM "CLONE IS A NEW METHOD TO TARGET SINGLE PROGENITORS AND STUDY THEIR PROGENY IN MOUSE AND CHICK," BY FERNANDO GARCÍA-MORENO ET AL., IN *DEVELOPMENT,* VOL. 141, NO. 7; APRIL 1, 2014 (*chick brain neurons*); FROM "MULTIPLEX CELL AND LINEAGE TRACKING WITH COMBINATORIAL LABELS," BY KARINE LOULIER ET AL., IN *NEURON,* VOL. 81, NO. 3; FEBRUARY 5, 2014 (*chick spinal cord neurons*)

What Really Causes Autism

The mystery is largely solved: autism is primarily a genetic disorder but a complex one that is slowly yielding its secrets

Seven actors stand around a circle of swirling colors—blue, gold and white painted in the middle of the stage. Interspersed among them are twice as many children. Most of the younger players look withdrawn. Many appear disabled, intellectually or physically. One girl, about 12 years old, sits quietly in an electric wheelchair. The professional cast take turns, enticing their young charges into the center of the colorful "island," where they play simple games—practicing facial expressions and chanting words—all based on emotional scenes from Shakespeare's play *The Tempest*.

By Simon Makin

Every child engages, even those who initially seem unreachable. Many react with unquestionable joy. It is possibly one of the most moving things I've ever witnessed. But this experience isn't really for the audience. My ticket reads: "*The Tempest,* Suitable for 8–24-year-olds with autism," and the production showcases a novel therapy for autism spectrum disorder (ASD). The approach—pioneered by Kelly Hunter of the Royal Shakespeare Company and developed in conjunction with psychologists at Ohio State University—is unproved. But the idea behind it is compelling: core abilities involved in drama match up strikingly well with what is often described as the main triad of impairments in ASD: problems with social interaction, communication and imagination. In short, the actors are gifted in the very things that are deficient in the young participants and able to reach powerfully across the divide of disability.

The diversity of the children onstage is a telling reflection of just how complicated autism is behind the scenes. An official diagnosis calls for the trio of difficulties described above, along with repetitive behaviors—typically hand flapping, rocking or head banging—before the age of three. That said, ASD sufferers exhibit a wide range of both physical and neurological symptoms. High-functioning people with autism, including those with Asperger's syndrome (a diagnosis that was recently cut from the American Psychiatric Association's manual of disorders), have normal and sometimes high IQs and often show only mild to moderate social deficits. At the other end of the spectrum, children with profound autism are often intellectually disabled and so socially detached that they seem locked in a world of their own.

Illustration by **ALEX WILLIAMSON**

In this special production of *The Tempest,* actors from the Royal Shakespeare Company showcase a novel therapy for autism.

Complicating the clinical picture, the condition often coincides with other diagnoses, such as anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), depression and epilepsy. According to the latest estimates, ASD affects one in 68 children. For decades researchers have debated its cause—an argument that grew increasingly urgent in the past 25 years as diagnostic rates soared. But recent studies have pretty well settled the question: autism is primarily genetic in origin, although it does not follow a simple hereditary pattern. Thanks to advances in DNA sequencing and collaborative efforts to pool data sets from laboratories around the world, scientists have found scores of genes that appear to be strongly linked to the disorder and many more that may also play supporting roles.

These new discoveries are offering important clues about the biology underlying ASD, insights that could eventually lead to targeted drug therapy. There is also a dawning realization that neurodevelopmental disorders in general—from autism to Down syndrome—may result not just from abnormal brain development but also from ongoing dysfunctional processes. The promise in that revelation is tremendous: although early interventions will remain vital in helping afflicted children reach their greatest potential, the hope is that even in adults, some aspects of ASD may one day be treatable.

Searching for the Cause

There is a saying common among people familiar with autism: "If you've met one person with autism, you've met *one* person with autism." This diversity is also proving true of the genetics behind the disorder. About one in 10 cases can be traced to mutations affecting a single gene. These so-called monogenic varieties generally occur as part of multifaceted syndromes that also cause physical malformations: fragile X, Phelan-McDermid, Rett and Timothy syndromes, as well as tuberous sclerosis and neurofibromatosis, to name a few.

Far more often ASD is considered idiopathic, meaning its root cause is unknown. Twin studies from as far back as the 1970s indicated that ASD was strongly heritable, but the subsequent rise in diagnoses led many researchers and parents to look for environmental influences. Currently experts believe that much of the increase stems from growing awareness among parents, pediatricians and educators and improved diagnostic criteria. Psychiatrist Terry Brugha of the University of Leicester in England and his colleagues found evidence in support of this idea in 2011, showing that a representative sample of previously undiagnosed adults had rates of ASD that were similar to recent estimates for children.

In recent years the evidence for genetic causes has

FAST FACTS

FIGURING THE ODDS

1. Thanks to recent advances in DNA-sequencing techniques and large-scale collaborations among laboratories worldwide, scientists have now identified scores of genes strongly linked to autism spectrum disorder (ASD).
2. Identifying specific causes is difficult because an individual's risk often comes from some combination of common and rare variants, many of which are inherited but some of which can be spontaneous.
3. The identification of ASD-linked genes is helping scientists to understand the biological processes involved in causing autism, which could lead to novel, more targeted treatment options.

LUCY BARRIBALL, © ROYAL SHAKESPEARE COMPANY

advanced dramatically. A barrage of studies has produced a steady stream of genes strongly linked to autism. Some estimate that the number of associated genes may ultimately top 1,000. One especially important discovery is the role that so-called de novo mutations play. These glitches in the genetic code occur spontaneously in a sperm or egg cell and so are not inherited from either parent.

In 2007 molecular biologist Michael Wigler of Cold Spring Harbor Laboratory, geneticist Jonathan Sebat, now at the University of California, San Diego, and their colleagues noted some of the first de novo mutations linked to ASD in the form of copy-number variants—alterations in chromosomes that involve the deletion or duplication of whole chunks of DNA, which can affect multiple genes. Soon other scientists started to find autism-linked de novo point mutations (also referred to as single-nucleotide variants because they are one-letter changes in the DNA) implicating specific genes. Since then, a rash of studies has homed in on several de novo mutations (both copy-number variations and single-nucleotide variants) that substantially raise an individual's risk for ASD—sometimes 20-fold and, in rare cases, even 80-fold.

At the same time, multiple studies found that de novo mutations increase with paternal age. For instance, in 2012 Brian O'Roak, then working in geneticist Evan Eichler's lab at the University of Washington, and his colleagues discovered that 80 percent of spontaneous point mutations occur within sperm cells and that the number of mutations tends to increase with a father's age. The findings explain a small percentage of the known increase in risk for autism among children of older fathers.

Last November two studies published simultaneously in *Nature* upped the total number of genes linked to autism from around nine to more than 70. Both investigations used a technique called whole exome sequencing, which focuses exclusively on exons, regions of the genome containing code for building proteins. This approach lets researchers quickly and more affordably screen the 1 percent of the human genome we know the most about. (*Scientific American Mind* is part of Springer Nature.)

The first report, by Wigler, Eichler, Matthew State of the University of California, San Francisco, and their colleagues, analyzed the exomes of more than 2,500 families from the Simons Simplex Collection, a set of DNA samples from so-called simplex families who, by definition, have only one child with autism. By comparing each child's genome with their parents', the researchers estimated that de novo mutations contributed to around 30 percent of ASD diagnoses in these families and to 45 percent of diagnoses in girls. They also identified 27 genes strongly linked to ASD.

NICK SPRATLING (*child with actor*)

Drama-based interventions capitalize on the fact that actors possess gifts kids with autism often lack—strong communication, imagination and social skills. Psychologists are studying whether rehearsing these abilities helps to develop them.

The second study came from the Autism Sequencing Consortium (ASC), involving researchers from 37 different institutions, by neuroscientist Joseph D. Buxbaum of the Icahn School of Medicine at Mount Sinai and his colleagues. Buxbaum—together with State, geneticist Mark Daly of the Broad Institute in Cambridge, Mass., and statisticians Kathryn Roeder of Carnegie Mellon University and Bernie Devlin of the University of Pittsburgh—founded the consortium in 2010, with support from the National Institute of Mental Health, to share samples and data. Looking for both inherited and spontaneous mutations, the team analyzed 3,871 autism cases and 9,937 unaffected individuals. They identified 33 genes strongly linked to ASD and more than 70 additional candidates. The genes implicated in these two studies overlap somewhat. Roeder reports that, along with geneticist Stephan Sanders of U.C.S.F., she has produced an unpublished list that includes genes affected by de novo copy variants. The top 71 of these genes are 90 percent likely to be involved in autism.

Adding Up the Risks

Most of the genes identified in the second study fall into three main categories. Some are involved in synaptic function—or how nerve cells in the brain communicate across the gaps, or synapses, between them. Some contribute to transcription, the process by which DNA is translated into proteins. And some play a role in remodeling chromatin—densely packed complexes of DNA and proteins whose changing structure determines which stretches of DNA are accessible for transcription. Because the latter two actually influence the activity of genes, they, too, may ultimately affect the growth and function of neurons and synapses.

A Genetics Glossary

Copy-number variations
Genes contain long series of "words" made up of the four DNA "letters" (adenine, cytosine, guanine and thymine), and sometimes these words—or entire paragraphs—are repeated once, twice or even 4,000 times. Such copy-number variations may be harmless or linked to specific diseases. Repeats of the three-letter sequence CGG on the X chromosome, for example, causes fragile X syndrome.

De novo mutations
Named for the Latin, "from the new," de novo mutations occur spontaneously in sperm, egg cells or fertilized eggs and are not inherited from either parent. The sperm of older fathers contains more de novo mutations, raising the risk of autism in offspring.

Epigenetics
Epigenetics refers to the study of gene-environment interactions, in which external factors—toxins, infections or even experiences—may change if and how certain genes are expressed. Once in place, these modifications can be passed down from one generation to the next.

Exome
The exome is that 1 percent of the genome containing exons, which are DNA sequences that carry the instructions for building proteins. The remaining 99 percent of the genome plays a regulatory role that influences how other genes function.

Genetic background
A gene's impact depends on interactions with other genes that make up a person's genetic background. This is why the same mutation can be benign in one person but cause disease in someone else.

Mitochondrial DNA
Inherited only through the maternal line, this DNA is found within mitochondria, the organelles that power our cells by converting chemical energy from food into a more usable form.

Point mutations
Also known as single-nucleotide variants, these mutations occur at a single DNA letter. They include one-letter swaps, deletions and insertions. Point mutations are implicated not only in autism but in cancer and color blindness, among other conditions.

Somatic mutations
These errors in the genetic code happen after conception during cell division. They can arise in any cell in the body except sperm and eggs. They multiply with cell division but are not inherited from one generation to the next.

Spontaneous versus inherited mutations
Inherited mutations are those that offspring share with their parents, but spontaneous mutations are unique to that individual. The genetic risk for autism appears to involve a mix of common and rare, inherited and spontaneous mutations.

These are mission-critical processes within and between cells, and so any disruptions during development could have far-reaching biological consequences. As such, these findings may explain evidence suggesting that ASD shares much of its genetic origins with other conditions, especially other developmental psychiatric disorders, such as schizophrenia, but also seemingly unrelated ones, such as congenital heart disorders. Researchers think that whether these genes actually trigger autism or something else or nothing at all may depend on the rest of a person's genetic makeup.

For instance, a specific high-risk mutation might potentially lead to a range of diseases or disabilities but will cause autism in those families whose inherited "genetic background" increases that particular risk. "There are some factors—not many—that increase risk enormously, some that increase it a lot, some that increase it some and a *lot* that increase risk a tiny bit," Buxbaum explains. "The manifestation of autism is the sum of all that risk in each individual, with some liability threshold, which differs for boys and girls."

More than four times as many boys are diagnosed with ASD as are girls. No one is exactly sure why, beyond assuming that girls are somehow protected from the effects of some mutations. A 2014 study by Sébastien Jacquemont, then at the University of Lausanne in Switzerland, and his colleagues found support for this idea, showing that affected girls tend to have more severe mutations. Also, these mutations were much more likely to have been inherited from the girls' mothers. One implication is that mothers can pass ASD-linked mutations on to their children without having the disorder themselves. These findings, together with the newly found importance of de novo mutations, may help explain why so many cases appear in families with no previous autism diagnoses.

De novo mutations seem to tip the balance in only about 14 percent of cases. Such severe mutations are rare precisely because they have a big effect and so reduce the likelihood of their carriers having children. "The usual reason a variant is rare is that it's brand-new in the population," Roeder says. Still, they offer a promising research avenue in that damaging genetic rarities often reveal more about the biological mechanisms of a disease than common, less harmful variants can. "We've learned a tremendous amount about cancer, hyperlipidemia, neurodegenerative disorders, and more through rare variations that account for a fleetingly small proportion of the population risk but have opened up compelling and widely applicable insights into biology," State observes. (For example, it was a gene for a rare, familial form of Parkinson's disease that led scientists to appreciate the role of the protein alpha-synuclein in all forms of the disorder.)

To date, researchers have had less luck nailing down the common genetic variations linked to ASD. Common variants collectively account for more of the risk of autism than rare ones do, but they individually confer such small increases that they are hard to identify. "At this point we have not pinpointed what specific common variants are relevant," says geneticist Benjamin Neale of the Broad Institute, who worked

Autism shares much of its genetic origins with other conditions, especially other developmental psychiatric disorders, such as schizophrenia, but also seemingly unrelated ones, such as congenital heart disorders.

on the ASC study. "But there are multiple reports that common variation has a substantial influence."

The interplay among different kinds of variation—rare, common, inherited and spontaneous—is key to understanding the genetics of autism, scientists say. This past February geneticist Stephen Scherer of the University of Toronto and his colleagues published the results of a study in which they sequenced the entire genomes of 85 so-called quartet families—two parents and two ASD siblings. It turned out that nearly 70 percent of these affected brothers and sisters had *different* rare variants previously linked with autism. Buxbaum speculates that these families may have different underlying risks because of common variation, which when combined with rarer, possibly spontaneous, variants push individual children over the ASD threshold. "I think that's what's going on," he says. "The family has increased risk, and then the two siblings have different final causes."

To try to parse the relative contributions of common and rare variations, Roeder and Devlin have developed statistical tools to extend the methods for estimating the heritability of a trait. Together with Buxbaum and his colleagues in the Population-Based Autism Genetics and Environment Study Consortium (PAGES), they evaluated more than 3,000 people from Sweden's universal health registry, including more than 450 with ASD. After their analysis, they estimated that 49 percent of the total risk for ASD stems from common variants, whereas only 6 percent is from rare mutations (3 percent inherited, 3 percent de novo). Other studies have shown that another 4 percent can be credited to things such as recessive genes. But that still leaves 41 percent unexplained.

From Genes to Biology

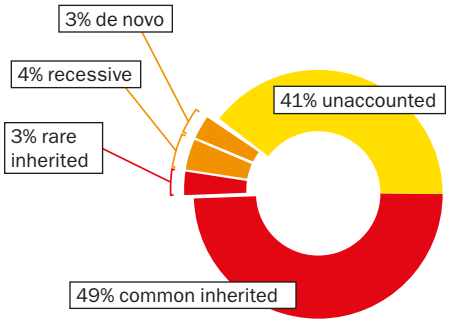
Some of this missing risk could reflect environmental factors—perhaps infections, or certain drugs or toxins in the mother's system during pregnancy, or birth complications—any of which might permanently alter the expression of genes (a gene-environment interaction known as epigenetics) or increase risk in other ways. But additional phenomena are involved, from random chance to somatic mutations, which are not present in the egg or sperm but arise in cells as they divide during development. In rare cases, autism has been associated with mutations in mitochondrial DNA, inherited exclusively through the maternal line. And the gut microbiome might be implicated. Some people with autism appear to harbor unusual communities of bacteria in the digestive tract that can produce waste that harms the brain.

Moreover, ASD genes do not act in isolation but interact with one another, the environment and other biological processes in complex ways we are only beginning to understand. All these additional factors help to explain why identical twins—who have nearly exactly the same DNA—are only somewhere between 80 to 90 percent likely to share an ASD diagnosis. (When they do not both have autism, the twin without it will often have another psychiatric diagnosis, such as ADHD.)

To find out where, and *when,* in the brain genes linked to autism interact and begin to cause problems, scientists are turning to cutting-edge projects such as the BrainSpan Atlas of the Developing Human Brain, developed by the Allen Institute for Brain Science in Seattle in collaboration with several universities. This dynamic atlas charts the activation of genes in the brain throughout development, from a fetus to an adult. Several recent studies have combined these data with genetic findings. In doing so,

What Are the Chances?

Scientists estimate that about 49 percent of the risk for autism comes from common genetic variants, another 3 percent from rare inherited mutations, 3 percent more from rare de novo mutations and 4 percent from recessive genes. That leaves 41 percent unexplained.



SOURCE: "MOST GENETIC RISK FOR AUTISM RESIDES WITH COMMON VARIATION," BY TRENT GAUGLER, ET AL., IN *NATURE GENETICS*, VOL. 46, NO. 8; AUGUST 2014

THE AUTHOR

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Even though identical twins inherit nearly exactly the same DNA from their parents, they are only somewhere between 80 and 90 percent likely to share an autism diagnosis.

researchers can map networks of genes that are expressed together in specific brain regions and cell types at the same time.

These investigations have revealed that many ASD-linked genes appear to function together in parts of the cortex during the mid- to late-fetal period, roughly five months after conception. Some studies specifically implicate what are known as projection neurons—cells responsible for forging long-range connections from one part of the brain to another. The finding bolsters some prominent theories that trace autism symptoms to abnormalities in how the brain is wired. Among those theories: there is an excess of local connections and insufficient long-distance ones.

Other scientists have considered not only where and when ASD genes are active in the brain but also how the proteins they produce interact. For instance, this past February systems biologist Lilia Iakoucheva of U.C.S.D. and her colleagues published findings from their investigation of an autism-linked copy-number variation known as 16p11.2. This stretch of chromosome 16 includes 29 different genes. Deletions increase the risk for autism; duplications increase the risk for both autism and schizophrenia.

Focusing on the genes found in this region, the team built up a related network of protein interactions. The researchers found that the protein produced by one 16p11.2 gene—called *KCTD13*—forms a structure with another protein, Cul3, during mid-fetal development. The *Cul3* gene lies in a different part of the genome but has been previously linked to autism in the form of de novo point mutations. Together these proteins control the levels of a third protein, RhoA, which is involved in choreographing the migration of cells in a developing brain.

The findings fit strikingly well with what was already known about how this mutation affects head size. When 16p11.2 regions are deleted, head size increases, whereas duplications decrease head size. (Larger than average head size is common among individuals with autism.) Iakoucheva says they were surprised to then find that mutations in a completely different gene, *CACNA1C*, which causes the rare form of autism called Timothy syndrome, have also been tied to this same RhoA mechanism. This convergence of three different mutations on the same biological process—one that might disrupt cell migration during fetal brain development—typifies much current thinking in the field: namely the suspicion that many of the 1,000 or more mutations that may be involved will ultimately converge on a limited number of underlying mechanisms.

The Path Ahead

Understanding exactly how ASD arises can only ease the anguish many parents have felt as they struggle to understand why the lightning bolt of severe autism happened to strike their family and worry that it will strike again. Scientists now have a set of genes they know will put a developing child

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As genetic testing improves, parents with one affected child will be able to gauge the risk to their subsequent children.

at high risk for ASD, a list that can only grow. These findings will eventually transform diagnosis and facilitate earlier interventions. As genetic testing for autism expands and improves, parents with one affected child will be able to determine the risks that subsequent children may face. If the dominant cause of ASD in a firstborn is a de novo mutation, it might suggest little or no increased risk. Inherited mutations, on the other hand, could up the odds to something as high as 50 percent. Prenatal testing may also eventually become available.

Ultimately the goal is to develop effective treatments. One reason the American Psychiatric Association replaced Asperger's syndrome and other subtypes with the generic term "autism spectrum disorder" is that biological evidence for the old subtypes was lacking. But as genetic findings help researchers to uncover the biological mechanisms involved, it may lead to more individualized approaches to treatment, as is already happening in other areas of medicine. It may be that one day the diversity of the kids I watched participate in *The Tempest* will be matched by a similarly diverse array of therapeutic options.

"Gene discovery is the thing we're trying to get done as quickly as possible before we get down to the real work of understanding the biology and pathogenesis of the disorder and where we can usefully intervene," Buxbaum says. The mechanism identified by Iakoucheva and her colleagues, for example, offers one possible treatment target. She and her collaborators plan to use stem cell technology to investigate whether an existing drug called Rhosin, which alters RhoA protein levels in nerve cells, might be helpful. If it works, researchers will still face the challenge of how to deliver the drug to fetal brains because Rhosin cannot cross the blood-brain barrier.

Researchers have also made great strides in understanding the molecular biology of monogenic syndromes such as fragile X and Rett syndromes and have developed interventions that show promise in animal models of these conditions, which were previously thought to be completely irreversible. "Finding out that, at least in animal models, you can erase many of the consequences, even in adulthood, is tremendously exciting," State says.

The discoveries have led to preliminary drug trials. Buxbaum and his colleagues recently published preliminary findings from an early-stage clinical trial of insulinlike growth factor-1 (IGF-1) in nine children with Phelan-McDermid syndrome, which is caused by mutations in *SHANK3*, one of the highest-risk ASD genes. In all the children, who ranged in age from five to 15, the growth factor—which enhances the maturity of synapses—improved social functioning and lessened repetitive behaviors, such as rocking.

Additional studies show that IGF-1 may also help children with Rett syndrome, but whether it will benefit more genetically complex forms of ASD remains an open question. Buxbaum cautions that these preliminary results need to be replicated in larger samples, but it is worth noting that IGF-1 crosses the blood-brain barrier. Other researchers are testing substances found to reverse deficits in fragile X syndrome and tuberous sclerosis to see if they might work in genetically complex cases.

At the moment there are many ways forward for autism researchers. Larger samples and better study designs will enable new variants with smaller effects to be found, and whole genome sequencing will make it possible for scientists to identify risky mutations in the large parts of the genome they have not yet fully explored. As the resolution of BrainSpan and similar resources improves, they may reveal more about how these genes shape the developing brain. Over the long term, this will lead to new interventions for a condition for which effective treatment has been elusive. "That's really what we're trying to do," Buxbaum says. "Everything else is just steps toward that goal." M

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- **The Contribution of De Novo Coding Mutations to Autism Spectrum Disorder.** Ivan Iossifov et al. in *Nature,* Vol. 515, pages 216–221; November 13, 2014.
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From Our Archives

- **Autism Grown Up.** Jennifer Richler; January/February 2015.

THE POSITIVITY EFFECT

As we grow older, we become more contented, despite the challenges of aging. New research is unraveling how and why the elderly "choose happiness"

By Marta Zaraska

When Lillian Fowler died in an Ohio nursing home at the age of 108, her relatives were quick to comment on how cheerful she had stayed until the very end. She had played golf into her 80s, became queen of the county fair at 104 and never stopped making friends. Her niece explains that Fowler chose to be happy no matter what her situation: "She would say, 'You need to blossom where you are planted.'"

Fowler's sunny disposition may counter our expectations for the elderly. After all, stereotypes of aging curmudgeons abound. But scientists researching longevity and aging suspect her story reflects a common pattern. Surveys and studies in developed countries around the world have given investigators a closer look at the relation between age and what psychologists call "emotional well-being"—that is, when a person consistently reports more positive than negative feelings. And by this measure, they have discovered that seniors are happier than their juniors.

In a classic 1995 study, for example, scientists at Fordham University categorized more than 32,000 Americans in age groups and found that 38 percent of seniors, aged 68 to 77, reported being "very happy," whereas younger groups were significantly less likely to report such positive feelings. In a study this year involving more than 10,000 Danes aged 45 and older, researchers at the University of Southern Denmark found that although seniors were considerably less healthy than younger adults, they were at least as happy.

And that contentment extends to those who,

MICHELLE PEDONE *Getty Images*

like Fowler, have crossed the century mark. British centenarians, questioned for a paper published in 2012, convinced psychologists that it "felt good to be 100 years of age." Iowa State University gerontologist Peter Martin, who has interviewed hundreds of people aged 100-plus, says: "Almost everybody I meet leaves me with a feeling that old age can be indeed a happy time."

These findings present us with a paradox: something about old age keeps people in good spirits despite hardships and physical decline. In fact, more than a decade of research findings have revealed that most elderly adults have an unfailing knack for focusing on the positive, whether in looking back at their memories or thinking about the present moment. Multiple hypotheses have emerged to explain this so-called positivity effect—including brain changes associated with the process of aging—but increasingly experts are coming to conclude that happiness is essentially a choice that older people make every day. Seniors with healthy minds make use of powerful strategies that let them tamp down negative experiences. In a sense, then, successful aging is largely about accentuating the positive.

Looking at the Bright Side

As researchers have wrestled with the correlation between happiness and age, numerous hypotheses have emerged and been debunked. Through a series of studies they have confirmed that the rise in contentment cannot be explained by reduced daily stress, although admittedly, elders are less burdened by work and child care duties than younger adults are. And even though happy people often outlive gloomy types, studies suggest that the happiness seen in older people reflects a change over time rather than a consistently sunny personality. Psychologists at the University of California, Irvine, and the University of Southern California followed up with more than 2,800 people for 23 years to chart how their emotional well-being changed with age. In 2001 the results came out: the older people got, the less they experienced negative feelings. In other words, the participants were becoming happier over time.

Then, in 2004, psychologists Laura L. Carstensen and Quinn Kennedy, both then at Stanford University, and gerontologist Mara Mather, now at the University of Southern California, stumbled on a different explanation. Back in 1987, Carstensen had questioned 300 nuns about their everyday lives. A second round of interviews followed in 2001 to check how well the sisters recalled what they had experienced 14 years previously. "The oldest nuns were remembering things as being more positive than they actually had been based on their original questionnaire," Mather says. This led the researchers to conclude that these older nuns exhibited an "age-related positivity effect," that is, an increasing tendency to concentrate on sources of happiness while downplaying negative information.

Hundreds of experiments have since corroborated this phenomenon. In a 2012 study, for example, psychologists Derek M. Isaacowitz and YoonSun Choi, both then at Brandeis University, invited 78 young adults (aged 18 to 25) and 77 older adults (aged 60 to 92) to his laboratory. He asked them to watch videos about skin cancer. While the volunteers watched the film, which was peppered with disturbing images of scars and scenes of surgery, special gaze-tracking equipment followed the move-

FAST FACTS

GET HAPPY

1. As people grow older, they tend to experience what psychologists call the age-related positivity effect—an increasing focus on positive events and happy feelings.
2. In imaging studies, elders who concentrate on joy have strong activity in circuits linking the amygdala, involved in emotion, and decision-making regions of the medial prefrontal cortex. Eye-gaze studies show that the older people look longer at upbeat images and away from upsetting ones.
3. Psychologists have found that when individuals of any age are reminded of life's fragility, their priorities shift toward emotional goals such as feeling happy and seeking meaningful activities.

GETTY IMAGES

Studies reveal that when shown disturbing scenes, seniors look away faster than young people do, **but they gaze longer at the good stuff: smiling kids, cute kittens, happy faces.**

ments of their eyes. The psychologists found that the older adults tried to distract themselves from the video's negative aspects—fixing their eyes significantly less on disturbing images than did teenagers or people in their 20s.

Similar studies have discovered that when seniors are shown pictures depicting negative situations (funerals, plane crashes, angry faces), they look away faster than younger people do. On the other hand, seniors fix their gaze longer on images of good stuff: smiling kids, cute kittens, happy faces. And just like their attention, the memory of older people is skewed toward the positive.

In a 2013 study, Mather and her colleagues showed YouTube videos of angry, happy and neutral faces to 21 seniors and 20 adults younger than 38 years. The volunteers watched the clips while lying inside a functional MRI scanner so that the scientists could see how different regions of their brain were engaged during the viewing. Two days later, when asked to recall which images they had previously seen in the scanner, seniors were more likely to remember happy images than angry ones, whereas younger adults were more likely to recall negative images. In addition, those elderly participants whose memories were particularly rosy had greater activity in circuits linking the amygdala (a part of the brain responsible for regulating emotion) and the medial prefrontal cortex (a region at the front of the brain involved in decision making).

Damaged Brain, Happy Brain?

Mather's 2013 experiment is one of many neuroimaging studies to show differences in brain activation between older and younger adults when they watch emotionally charged images—particularly in the amygdala and the prefrontal cortex. These findings suggest that age-related changes in the brain may contribute to the positivity effect in old age. Another line of evidence comes from a new twist on an earlier study related to happiness across a life span. In 2008 labor economist Andrew Oswald of the University of Warwick in England and David G. Blanchflower of Dartmouth College discovered the famed U-shaped curve of happiness. Their data set, encompassing half a million people in 72 countries, suggested that over the course of life, our emotional well-being follows a predictable pattern: starting high, hitting a trough in midlife, then climbing upward again in later years. In a surprising update to this finding, Oswald and his colleagues at multiple institutions found in 2012 that zookeepers see chimpanzees and orangutans exhibit more happy behaviors—such as indulging in pleasurable socializing—at the beginning and end of their lifetime. In other words, at least according to their caretakers, the well-being of apes also follows the U-shaped curve. According to Oswald, this observation hints that something biological is at work across species in the correlation between age and happiness.

More potential evidence that brain changes underlie happiness in seniors came from a 2015 study by University of Toronto psychologist Cheryl Grady and her colleagues. Grady put volunteers in an fMRI scanner and discovered that seniors with the most decline in their so-called default network of the brain—a set of interconnected regions that plays a role in introspection and memory retrieval—are more likely to think positively about themselves compared with seniors who do not show this decline. "This suggests a link between a weaker activity in this network and the positivity effect in older adults," she says.

So what *is* going on? In 2011 University of Chicago neuroscientist John Cacioppo and his colleagues speculated that age-related damage in the brain—in the amygdala in particular—might contribute to well-being in later life. To support his theory, Cacioppo points to the finding that negative events or stimuli do not strongly arouse the emotions of people who have lesions on the amygdala, yet these individuals can be excited by positive things.

Zookeepers have noticed that chimpanzees and orangutans appear to be happier—indulging in more social behaviors, for example—at the beginning and the end of their lifetime. Humans appear to follow a similar pattern.

Yet the aging brain model cannot fully explain the positivity effect. Brain damage, after all, has negative consequences that diminish well-being. Take Alzheimer's disease. It harms both the amygdala and the default network. If aging-related declines in such regions were the main reason why seniors were so contented, one might expect Alzheimer's patients to be a particularly cheerful group. They most certainly are not. In addition, the amygdala does not sustain very much damage in nor-

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JAMES BALOG *Aurora*

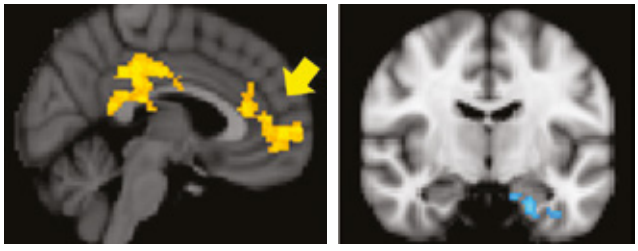
mal aging. "The amygdala is the region of the brain that's centrally engaged in emotion processing. And of all the regions of the brain, it is among the best preserved until very advanced age," Carstensen says.

Another problem for the brain-degeneration theory of happiness is that the seniors who show the strongest positivity effect are also the ones whose minds are the sharpest. In a study published last August, a group of scientists at the University Medical Center Hamburg-Eppendorf in Germany checked attention to positive and negative images in 25 older and 25 younger adults and then tested their cognitive abilities. The results were clear: seniors with the most cognitive resources—that is, those who had strong mental abilities across tests—demonstrated the strongest positivity effect. Perhaps certain brain changes do contribute to this effect, but an impaired mind does not add much glow to the golden years.

> Seniors who have the sharpest minds show the strongest positivity effect, **belying the theory that late-life contentment is the product of a deteriorated mind.**

Choosing Happiness

The fact that seniors need cognitive resources to stay positive points to an earlier explanation for elderly people's penchant for positivity. According to socioemotional selectivity theory developed in the past 23 years by Carstensen and her colleagues, seniors are more satisfied with their lives because they *want* to be more satisfied with their lives. As they see the end of life approaching, they start focusing on what feels good instead of acquiring knowledge. The first clue that seniors increasingly reshape their world to make it more pleasant came from Carstensen's 1992 study in which she analyzed interviews conducted over 34 years with 50 people. She showed that the older we get, the narrower our social circle becomes because we engage mainly in relationships that we find most satisfying—and end up happier as a consequence.



In 2013 University of Southern California researchers found that certain brain areas were strongly active in older individuals who were particularly upbeat, specifically the medial prefrontal cortex (*indicated by yellow arrow in left image*) and the amygdala (*blue area in right image*).

More recent work extends this idea. In an experiment published in 2013 by University of California, Berkeley, psychologist Iris Mauss and her colleagues, older people were less anxious than young people when they had to give a speech in front of a camera. The difference in this case reflected the fact that the older individuals showed more acceptance of the task and were less caught up in self-conscious or self-critical emotion. In another experiment, after "accidentally" overhearing negative remarks about themselves, seniors reported less anger than did participants in their 20s or 30s.

Carstensen and other psychologists believe that this behavior reflects a change of goals. Aware of life's fragility and their own mortality, people concentrate more and more on regulating emotions to maximize good feelings in the time that is left. This tendency does not negate the possibility of changes in the brain related to aging but does place more emphasis on psychological processes. "Younger people think: 'I have to finish school, I have to get a job.' Older adults don't have these sorts of pressures any more. They are more focused on interpersonal relationships and basically just enjoying the rest of their lives," says Cheryl Grady, who, like most researchers in the field, suspects both biological changes and psychological choices can explain the positivity effect.

Furthermore, this shift in priorities is not limited to the elderly. Carstensen and her colleagues have found it in young HIV sufferers and, more surprisingly, in people who start perceiving life as fragile because of major disasters, such as the tragic events of September 11, 2001. That young people may experience this change further wrinkles the theory that brain declines drive the positivity effect. It is even possible that the brain differences scientists have observed in fMRI studies may be a consequence of a person's attempts to stay positive, not the cause.

Whether people consciously choose to look on the bright side is unclear—but we do know that keeping positive in the face of negative events requires some effort. That is why cognitive resources are required—if you exhaust a person's resources or direct them toward another task, the positivity effect is lost. For example, Mather has found that when you tax the brain by distracting someone during an activity, older adults will lose their rose-colored glasses. "We did a couple of studies where we had older adults using their prefrontal cognitive resources to remember some other information, so they couldn't control what they were paying attention to, and the negative things really stood out for them just like they did for the younger adults," Mather says.

But provided they do have the cognitive energy to expend, seniors are masters at regulating emotions. One strategy that helps to steer them toward the positive is self-distraction in the face of a negative experience. A study published in May showed that older people are skilled at thinking about something unrelated to the negative situation they encounter. An internation-

FROM "AMYGDALA FUNCTIONAL CONNECTIVITY WITH MEDIAL PREFRONTAL CORTEX AT REST PREDICTS THE POSITIVITY EFFECT IN OLDER ADULTS' MEMORY," BY MICHIKO SAKAKI ET AL., IN *JOURNAL OF COGNITIVE NEUROSCIENCE*, VOL. 25, NO. 8; AUGUST 2013

JOSE L. PELAEZ *Corbis*

al team of researchers—based at the University of Groningen in the Netherlands, Tel Aviv University and Columbia University—gave 39 seniors and 38 younger participants unpleasant photographs to examine (of a burned woman, for example), then asked them to either distract themselves, by thinking about everyday chores such as grocery shopping or making coffee, or attempt to interpret the images' content in a way that gave them a positive emotional meaning (for example, imagining that a photograph of a crying baby was taken minutes after a lifesaving inoculation). Elders opted for distraction significantly more often than younger adults did.

Diverting one's gaze works as well. In Isaacowitz's skin cancer study, seniors who looked away from disturbing images felt better in the end. And if you cannot look away or distract your thoughts, you can try to accept the negative experience, which research suggests can diffuse sensations of anxiety more effectively than simply suppressing those feelings. Older people tend not to think of their emotions as inappropriate or bad. That stance contributes to well-being, too.

Using similar techniques, Carstensen, Mather and Isaacowitz have shown that younger adults can be trained to look more at the bright side of life, at least temporarily, which boosts their contentment. Still, this approach does not mean young people should routinely rely on such strategies. "Every time I give a talk about these age differences, some young person comes up to me and asks, 'How do I get to be like an old person?' And I say, 'I don't think it's a good idea. You *do* have to prepare for a long future. You *do* have to encounter conflict to achieve a long-term goal.' That's highly adaptive," Carstensen says.

In other words, the Zen-like mind-set of our later years involves a trade-off. If you have much to learn, do and achieve, then you need some negativity in your life. A young professional, for example, should acknowledge a co-worker's critiques, and new parents need to learn about potential dangers to their children—even if the knowledge is distressing. Detaching oneself from the world's harsh realities is a luxury that not everyone can afford.

But there are things that people of all ages can and should do to ensure happy futures. The combined biological and psychological evidence makes it clear that to profit from positivity effects in old age, you need good cognitive resources. So, *do* care for your body and brain. Eat well. Exercise. Challenge your intellect. Many people spend their lives chasing happiness or a sense of contentment. It turns out that time itself could be the secret formula—provided you take care of your mind. **M**

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- **Emotion and Aging.** Mara Mather and Allison Ponzio in *The Handbook of Emotions.* Fourth edition. Edited by Lisa Feldman Barrett et al. Guilford Press (in press).

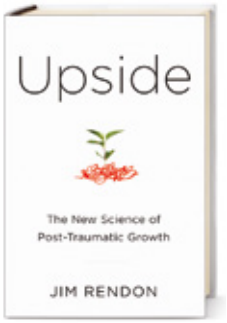
From Our Archives

- **How to Control Your Feelings—and Live Happily Ever After.** Steve Ayan; January/February 2015.
- **Debunking Midlife Mysteries.** Hanna Drimalla; March/April 2015.

BAD IS GOOD

Upside: The New Science of Post-Traumatic Growth

by Jim Rendon. Touchstone, 2015 ($26; 288 pages)



"God let me live for a *purpose.*" So I was informed, emphatically, by a fireball of a woman named Dr. Ruth Westheimer the first time I met her—all 4'7" of her. The renowned sex therapist, author and media personality lost most of her family in the Holocaust, and she has been driven ever since to make her positive mark on the world. For years billionaire talk-show host and entrepreneur Oprah Winfrey was sexually abused by multiple male family members and friends of her mother. She not only survived her harrowing childhood, she used the pain inside her as a springboard to success.

Are these two women's experiences just flukes, or can trauma sometimes be beneficial? Opening with the story of his father's dramatic escape from a concentration camp in 1945, Rendon, a freelance journalist, answers this question in two eye-opening ways. First, he suggests that trauma may be the driving force behind the accomplishments of many influential, passionate people, and second—and this is the bigger surprise—that a wealth of recent research shows that what we usually think of as the inevitable outcome of trauma—posttraumatic stress disorder (PTSD)—is in fact the exception to the rule. Simply put, more people *benefit* from trauma than are harmed by it.

Upside is a rich and detailed follow-up to a 2012 article Rendon wrote for the *New York Times Magazine* about trauma's "surprisingly positive flip side." It is a tapestry of poignant stories about a wide range of people who have triumphed over agonizing losses—of children, spouses, limbs, fortunes, careers, dreams—interwoven seamlessly with the results of dozens of relevant scientific studies and stories about the pioneering researchers who conducted them. The most intriguing analyses suggest a close symbiotic relation between trauma and creativity: trauma forces people to solve daunting problems (think "necessity is the mother of invention"), and the expression of creativity is itself therapeutic (Henri Matisse, Frida Kahlo and Maya Angelou were all trauma survivors).

It has been known for millennia that trauma can have positive benefits, but it wasn't until the 1980s that "post-traumatic growth" was first studied methodically, primarily by two then maverick psychology professors: Richard Tedeschi and Lawrence Calhoun, both at the University of North Carolina at Charlotte. Rendon tracks their journey—at times, a difficult one, given the overwhelming power of PTSD to grab headlines and research funding—on the road to documenting the indisputable benefits that trauma can have to strengthen relationships, spur creativity, and add meaning and deep purpose to people's lives.

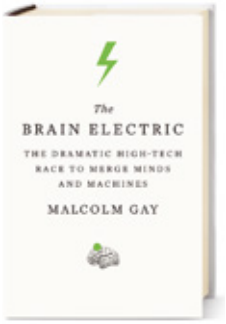
Trauma is, in Rendon's words, "transformative." It is a "dividing line," he says, but not necessarily harmful. If you are looking for inspiration, perspective and some unexpected science, *Upside* is a good choice.

—Robert Epstein

BRAIN WARS

The Brain Electric: The Dramatic High-Tech Race to Merge Minds and Machines

by Malcolm Gay. Farrar, Straus and Giroux, 2015 ($26; 288 pages)



In one of the most memorable scenes from the early *Star Trek* movies, Dr. Leonard McCoy confronts a 20th-century surgeon, who is about to drill holes in *Enterprise* navigator Pavel Chekov's head, and gives him a dressing-down, roaring about the era's primitive "butcher knives." McCoy soon repairs Chekov's badly damaged brain with a high-tech gizmo from the future that looks like an Xbox and doesn't even break the skin.

Hold that image in mind—of the extreme contrast between the primitive present and the supposedly wondrous future—and you will begin to understand why journalist Gay's *The Brain Electric* is, all at once, one of the most fascinating and exasperating books you will ever read. Why? Because it is about the almost unspeakably primitive drills and butcher knives that some of today's leading scientists are using to try to bring about the extraordinary future we so often picture in science-fiction movies.

To get to a future in which someday, maybe, people will communicate with computers, the Internet and even one another using their thoughts alone—no more keyboards, mice, telephones or shouting at your kids down the block—you need to start somewhere, right? Gay takes us into the gritty labs of the surgeons who have been doing the hard work for the past 15 years: Andrew Schwartz of the University of Pittsburgh, Miguel Nicolelis of Duke University and others. They all are in cutthroat competition for the next big DARPA grant and, of course, for the brass ring—the Nobel Prize that is almost certain to be awarded to the best of the lot.

And talk about grit. Gay takes us step by gruesome step through procedure after procedure in which cocksure docs breach skulls and implant arrays of electrodes into the brains of rats, monkeys, and paralyzed and epileptic humans in brazen attempts to get neurons communicating meaningfully with computers. Occasionally there is a breakthrough: a paraplegic woman thinks a robot arm to feed herself; a monkey whose arms and hands are restrained plays a video game; the brains of two rats are linked in a way that gets the actions of one to affect the actions of the other.

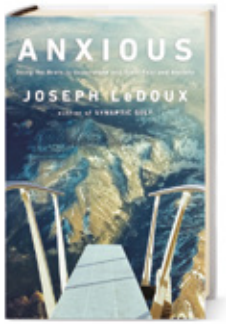
So amazing, so promising—and so frustratingly primitive. The brain has 100 billion neurons, but even the most sophisticated implants can monitor only a few hundred. Within weeks or months the immune system invariably attacks the implanted electrodes, rendering many of them useless, and the brain changes so rapidly that connections often have to be recalibrated daily to keep them working properly. There are no cures, no miracles—only suggestive demonstrations, foretelling—who knows, really?

The book ends with a sobering reminder of just how rudimentary present-day brain science is. Gay quotes Schwartz: "We have no idea what makes a neuron fire…, and that's at the root of everything." But you have to start somewhere, right? *—R.E.*

VICIOUS CYCLE

Anxious: Using the Brain to Understand and Treat Fear and Anxiety

by Joseph LeDoux. Viking, 2015 ($28.95; 480 pages)



Woody Allen's character in *Annie Hall* is not Hollywood's typical leading man. Alvy Singer may be charming and witty, but he is so preoccupied with the minutiae of his diet, past romantic debacles and the eventuality of his death that he ultimately drives away his girlfriend, Annie.

Allen was one of several cultural figures to embrace anxiety in the 1960s—it was "the centrifugal force of his cinematic humor," according to LeDoux, a world-renowned expert on memory and emotion and professor at New York University. LeDoux reassures us that anxiety is a natural part of life, although, for many, it becomes pathological. The Anxiety and Depression Association of America estimates that 40 million U.S. adults suffer from an anxiety disorder.

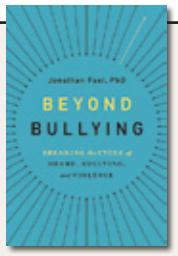
In *Anxious,* LeDoux explores cutting-edge research on the biology, neuroscience, and psychology of anxiety and fear in an effort to unravel what anxiety is, how it can become a harmful, sometimes debilitating condition, and how we should treat it and related disorders. Contrary to popular belief, LeDoux argues that anxiety is not an innate response. Instead our life experiences seed its development over time. More specifically, he says, the physiological responses associated with anxiety—sweaty palms, tense muscles and heart palpitations, for instance—eventually change our brain chemistry.

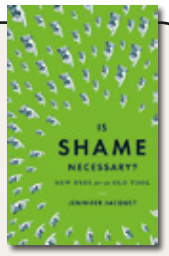
LeDoux explains that fear and anxiety overlap in many ways, but they differ in a few key respects. Fear is triggered by a direct threat, whereas anxiety is much more insidious, arising in response to a perceived threat. We may become anxious when we think about a hypothetical future scenario or recall an unpleasant memory. In this way, anxiety holds great power over our minds and behaviors because it spans our past and future as well as our present.

Anxiety reaches the level of a disorder, LeDoux says, when a person has amassed a certain threshold of mental and physical symptoms that regularly influence his or her decisions and actions. Someone afraid of heights, for instance, may go through great pains to avoid taking an elevator, climbing stairs or even looking out a window.

The second half of the book focuses on current and future remedies. According to LeDoux, the drugs available to treat anxiety disorders fall short because they address only our overactive neural response, not the underlying associations. What we need, he argues, is a multipronged approach that can recondition our response to triggers. Current efforts focus on tweaking a person's neural environment—applying electrical stimulation or using hormones such as oxytocin—while he or she is feeling anxious in an effort to change bad associations into good or neutral ones.

Overall, LeDoux provides one of the most complete portraits of this complex emotion. Unfortunately, *Anxious* can read like a textbook—which is how it was originally conceived—making it challenging, at times, for a nonscientist to fully grasp the content. Still, LeDoux largely makes up for this shortfall by weaving in lighter moments—including fun narrative asides from his own life and intriguing forays into philosophy and animal psychology. These threads help to place anxiety and related disorders in a personal and historical framework, not just a clinical one. *Anxious* is a fascinating book with breadth that extends beyond its title. *—Alexandra Ossola*





ROUNDUP

The Spiral of Shame

Three books explore the science of public humiliation

Social media has the power to shame people in just a few clicks. Take former public relations executive Justine Sacco, who jokingly tweeted an offensive comment about AIDS and Africa, or charity worker Lindsey Stone, who while on a work trip broadcast a photograph on Facebook in which she appeared to be mocking dead war veterans. Their posts went viral, receiving thousands of comments from strangers who condemned and threatened Sacco and Stone. Both women lost their jobs, their friends and their dignity. In **So You've Been Publicly Shamed** (Riverhead Books, 2015; 304 pages), journalist Jon Ronson, author of *The Psychopath Test: A Journey through the Madness Industry,* explores high-profile examples of how making a mistake on social media can ruin your life. In fact, the unbridled shaming, Ronson says, far surpasses any actual or apparent transgression. In his book, he shines a light on this trend of online bullying, highlighting how this form of harassment has become particularly easy and vicious via posts on social media sites.

Sometimes shaming, whether it's online or in person, can be fatal. In **Beyond Bullying: Breaking the Cycle of Shame, Bullying, and Violence** (Oxford University Press, 2015; 256 pages), Jonathan Fast, associate professor of social work at Yeshiva University, describes the dark underbelly of shame. Fast admits that at low levels, shame can be beneficial—signaling, for instance, when we have behaved inappropriately—but when unhinged, it can become a weapon. Fast delves into the psychology and sociology of shame and concludes that this powerful emotion is *the* common thread explaining the recent rise in domestic terrorism and gun violence, school and online bullying, and suicide among adolescents. He hopes that by understanding shame—why we feel it and how it can fester—we can develop strategies to prevent the acts of violence and hate that are motivated by it.

But is it possible to put humiliation to good use? In **Is Shame Necessary? New Uses for an Old Tool** (Pantheon, 2015; 224 pages), Jennifer Jacquet, an assistant professor of environmental studies at New York University, argues that shame can be an effective, nonviolent tactic to promote positive change if targeted appropriately. Shaming powerful groups (governments and corporations) or dominant individuals (CEOs and the wealthiest 1 percent in the U.S.) may help us challenge potentially harmful decisions or behaviors and promote political and social reform. *—Victoria Stern*

Why do people discard scientific rigor in favor of someone's opinion?

—Peter Gutmann, New Zealand

Keith E. Stanovich, an emeritus professor of applied psychology and human development at the University of Toronto, answers:

Decades of research have shown that humans are so-called cognitive misers. When we approach a problem, our natural default is to tap the least tiring cognitive process. Typically this is what psychologists call type 1 thinking, famously described by Nobel Prize–winning psychologist Daniel Kahneman as automatic, intuitive processes that are not very strenuous. This is in contrast to type 2 thinking, which is slower and involves processing more cues in the environment. Defaulting to type 1 makes evolutionary sense: if we can solve a problem more simply, we can bank extra mental capacity for completing other tasks. A problem arises, however, when the simple cues available are either insufficient or vastly inferior to the more complex cues at hand.

Exactly this kind of conflict can occur when someone chooses to believe a personal opinion over scientific evidence or statistics. When we evaluate a personal opinion, we automatically engage the evolutionarily old regions of the brain, which encourage social interaction and peer bonding. But understanding scientific evidence, a more recent achievement, involves more complex, logical and difficult type 2 processing.

From this dual-processing perspective, we can see several ways in which personal opinion might trump scientific thinking. First, some people may not have learned the rules of scientific thinking. In such cases, type 1 processing will be their default setting. And even if we can evaluate concrete evidence, our tendency to revert to type 1 processing may still lead us astray, ignoring logical reasoning in the face of an emotionally persuasive personal opinion. In other words, even when scientific thinking is compelling, our propensity to be a cognitive miser and conserve mental energy often prevents us from engaging type 2 processes.

The good news is that it is possible to override our tendency toward type 1 processing. To do so, we must practice scientific and statistical thinking to the point of automaticity, eventually making it our go-to option.

What happens to the brain when we experience cognitive dissonance?

—Thea Buckley, India

Keise Izuma, a lecturer in the department of psychology at the University of York in England, replies:

Cognitive dissonance is that uncomfortable feeling you get when you try to maintain two or more inconsistent beliefs at the same time or when you believe one thing but act in a contradictory way. For example, you commit to losing weight and then gorge on cake. The discrepancy can be unnerving, and people will often try to eliminate the dissonance by changing their attitudes. So to feel better about cheating on our diet, we may tell ourselves that we will go for a run tomorrow.

What is the neural explanation for this common type of psychological stress? Thanks to advances in imaging methods, especially functional MRI, researchers have recently identified key brain regions linked to cognitive dissonance. The area implicated most consistently is the posterior part of the medial frontal cortex (pMFC), known to play an important role in avoiding aversive outcomes, a powerful built-in survival instinct. In fMRI studies, when subjects lie to a peer despite knowing that lying is wrong—a task that puts their actions and beliefs in conflict—the pMFC lights up.

Recently my colleagues and I demonstrated a causal link between pMFC activity and the attitude change required to reduce dissonance. We induced cognitive dissonance in 52 participants by having them rate two wallpapers. When asked to evaluate their choices on a second viewing, some participants realized that they had actually rejected their preferred wallpaper, whereas others had initially chosen their least favorite option. We found that by temporarily decreasing activity in the pMFC using a technique called transcranial magnetic stimulation (TMS), we could also diminish their attitude changes and their desire to create consistency.

Additional studies have revealed that cognitive dissonance engages other brain regions, such as the insula and dorsolateral prefrontal cortex (DLPFC). The insula, which processes emotions, often becomes more active when people are upset or angry, and the DLPFC is strongly associated with cognitive control. One study found that disrupting the activity of the DLPFC by zapping it with electrodes reduces the extent to which we try to rationalize our beliefs following cognitive dissonance.

Although people may think cognitive dissonance is a bad thing, it actually helps to keep us mentally healthy and happy. It may make us feel satisfied with our choices—or at least lets us justify them—especially when they cannot be easily reversed. Resolving dissonance may help prevent us from making bad choices or motivate us to make good ones. This desire to be at peace with our decisions might be just the thing to inspire us to go for that run after all. **M**

JAMIE CARROLL ©iStock.com

1 WORD CLOCK

An eight-letter word is spelled out in the box below. Find it by beginning with the correct letter and moving clockwise or counterclockwise around the box, using each letter only once.

E	R	E
N		H
T	A	D

2 MAGIC SQUARE

Fill in the square below with two Es, one V, four Rs, one S and one A so that common English words can each be read across and down.

C	O	D	E
O			
D			
E			

3 PUZZLING PATTERN

The following series is dictated by one rule. Find the rule and fill in the missing number.

94 26 16 14 ?

4 MIND THE REMAINDER

This subtraction problem uses each of the digits from 0 to 9 once and once only. Three numbers have been filled in to give you a head start.

? 0 ? 5
– ? ? ?
? 4 ?

5 ODD ONE OUT

Unscramble the following words. Which is least like the others?

PELIPPAEN NNAAAB WKUIIIRTF OAOTTP

6 ONE LETTER OFF

In each row, think of the five-letter answer to the clue on the left, then change its second letter to make the five-letter answer to the clue on the right.

a) Roof overhangs _____ **North Pole workers** _____
b) Grassy cluster _____ **Patsy** _____
c) High-tech beam _____ **Runner-up** _____

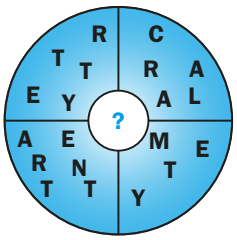
7 SENTENCE SNAKE

A statement about someone's smarts is coiled in the grid below. To spell it out, start with a "T" and move to an adjacent letter in any direction. All letters will be used exactly once. (Hint: The enumeration is 3 5'1 2 3 6'1 4.)

E	H	S	E	T
M	O	Y	L	H
B	O	D	I	G
O	U	B	T	H
N	T	N	O	S

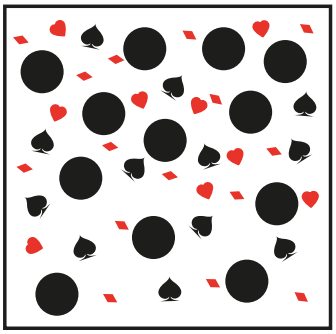
8 MISSING LINK

Reorder the letters in each "pie" segment below, then find the missing letter that completes each word. (Hint: The missing letter, indicated by the question mark, is the same for each word.)



9 DIVIDE AND CONQUER

In the diagram below, use two straight lines to divide the square into three sections. Each must contain four circles, five diamonds, four spades and three hearts.



10 MINI CROSSWORD

1	2	3	
4			5
6			
	7		

Across
1 Locker?
4 Fateful day
6 Watch face
7 Stab

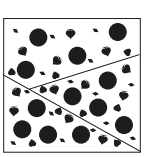
Down
1 Youngster
2 Blue pencil
3 2008, e.g.
5 Artful

Answers

10.

K	E	Y	
I	D	E	S
D	I	A	L
	T	R	Y

9. The missing letter is "P": CARPAL, EMPTY, PATTERN, PRETTY.



8. The others are PINEAPPLE, BANANA and KIWIFRUIT.

5. POTATO. The others are vegetables.

7. The light's on, but nobody's home.

6. a) Eaves, Elves; b) Clump, Chump; c) Laser, Loser.

4. Here is one solution:
1,035
– 786
249

3. 10. Each successive number is obtained by adding the two digits of the previous number and multiplying by 2.

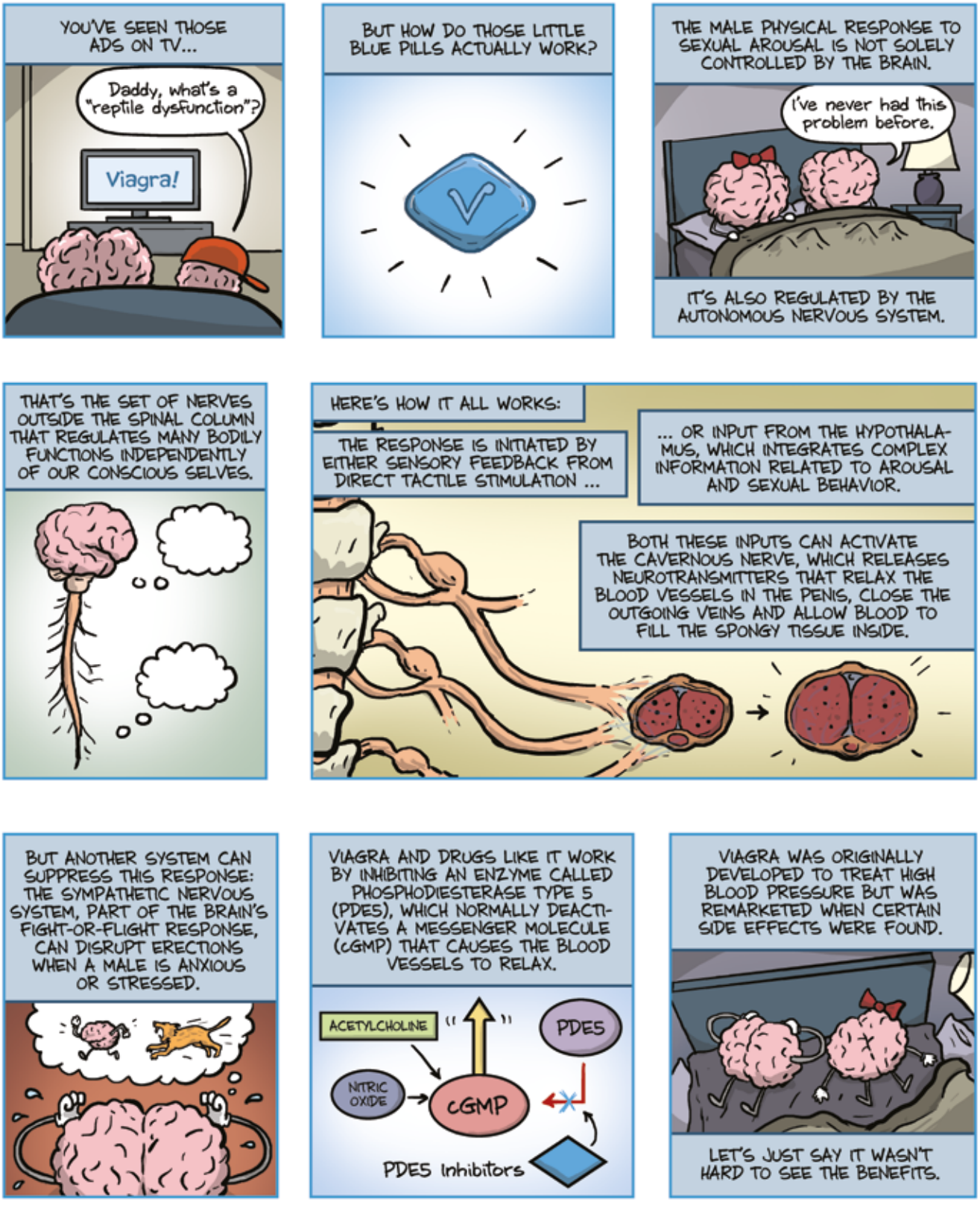
1. ADHERENT.

2.

C	O	D	E
O	V	E	R
D	E	A	R
E	R	R	S

The Blue Pill

BY DWAYNE GODWIN & JORGE CHAM



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

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