HAPPIER TEENS: THE DIFFERENCE A DAD CAN MAKE *page 44*

SCIENTIFIC AMERICAN MIND

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7 Amazing Illusions That Fool Your Brain

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SPECIAL REPORT

THE SCIENCE OF MEMORY

WHAT CAN GO WRONG—AND HOW YOU CAN STAY SHARP

PLUS

A New Theory of Consciousness

Stem Cells for Parkinson's

Cameras That Work Like Eyes

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COVER IMAGE BY AARON GOODMAN; SEAN McCABE (*Upson*)

Keeping Memories Alive

When I was eight years old, my family moved out of our 100-year-old house in the Netherlands. Its ivy-covered brick walls, dark green door and matching window shutters remain vivid to me. I still keep a framed photo of my golden retriever and me scampering down the pebble driveway, which led past rhododendrons to a separate garage. Behind it rose a majestic dune.

The passing of decades inevitably weakens the brain connections that hold such slices of time in place. Yet as I learned in this issue's special report, "How We Remember," revisiting one's recollections helps the brain rebuild aging neural links. In "The Engine of Memory," psychologist Donald G. MacKay describes his discovery of several ways the mind repairs and strengthens reminiscences. Turn to page 30.

Also in the report, cognitive scientist Felipe De Brigard delves into the mystery of the hippocampus, a brain region viewed as the seat of memory. People with damage to this area develop amnesia—but also suffer deficits of imagination, sight and other core mental functions. Connecting with our past makes it easier to envision the future, it seems. See "The Anatomy of Amnesia," beginning on page 39.

Memory is not the only faculty vulnerable to the ravages of time and disease. New hope for treating disorders in which brain cells perish, such as Parkinson's, is now emerging in the form of stem cell therapies. Starting on page 59, journalist Lydia Denworth reports on stunning progress in cultivating replacement neurons. The advances she describes in "The Regenerating Brain" demanded many years of painstaking research—a reminder that the passage of time also brings us breakthroughs that improve human lives.

Last October, I paid a brief visit to the house in the Netherlands, my first trip back in decades. I recognized the facade, but gone were the green shutters and the ivy, as well as the detached garage. The gardens had been transformed. The building was a stranger now, not a friend. Yet it dawned on me that my beloved childhood home still stood safely in my memories. By carrying the past forward with us, our present and future become all the richer.

Sandra Upson
Managing Editor
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VOLUME 25, NUMBER 3, MAY/JUNE 2014

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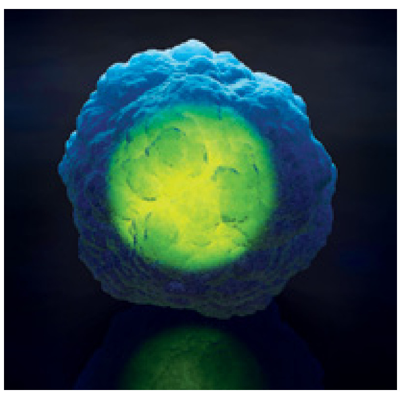
FEATURES

SPECIAL REPORT HOW WE REMEMBER



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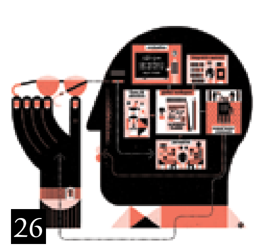

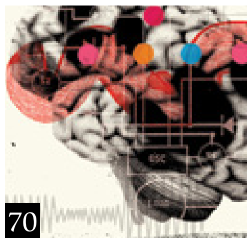

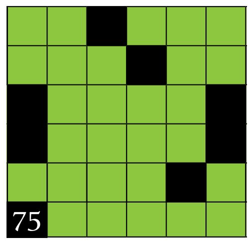

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LETTERS JANUARY/FEBRUARY 2014 ISSUE

INNER SPEECH

"Speak for Yourself," by Ferris Jabr, is astounding in its implications. Helen Keller said she didn't have self-awareness or consciousness before she met her teacher and learned language. An aphasic stroke victim who loses inner dialogue loses the ability to structure thoughts in terms of past and future and so can only exist.

Is it possible that the evolution of a primitive language predated the expansion of the human brain and our rise to lofty heights of intelligence? What if we hit a tipping point of rudimentary language that allowed us, as with Helen Keller, to become self-aware for the first time and begin to structure our thoughts and world in a more complex way, with past and future, layered emotion, and a capacity for structured planning?

And have we ourselves already done this experiment unwittingly? We have taught gorillas to use sign language so they could tell us how they think. But what if the act of teaching them a language fundamentally changed the way that they actually thought? What if we then saw not the intelligence of the average gorilla but rather a gorilla that was endowed with a heightened ability to reason beyond that of any other gorilla that ever existed? What an amazing example of observer effect!

Jeremy Fox
Singapore

JABR REPLIES: *Fox has some fascinating ideas. Although human self-awareness seems to depend on verbal thought, that does not mean other animals construct self-awareness in the same way. No one definitively knows the difference between self-awareness and consciousness because consciousness is still such an ill-defined concept, but one could imagine a person or creature that is conscious—aware of its surroundings—yet does not understand that it has a "self." It is possible that the young Helen Keller, stroke patients who have lost all inner speech, and even newborns fall into this category: certainly conscious, even without language, but not self-aware.*

DISORDER OR DIFFERENCE?

Here we go again. In "Taking Early Aim at Autism," by Luciana Gravotta, I am being told before I even start to read the article that I have a "developmental disorder" and "deficits that will become debilitating." The only trouble is, I am almost 89 years old, and when I was an infant no one told my mother about my "condition." But my mother was a wise woman who managed to steer me through those awkward years when I did things like saying in a loud voice, "That lady is fat." She allowed me to take an alternative route when pneumatic drills on the road terrified me. She worked out ways of managing my various behaviors, remarkably similar to those strategies now advised by experts working with children with autism.

I eventually managed to qualify as a medical practitioner and worked at my trade for nearly 40 years, still blissfully unaware of my "disorder." In fact, I had already been retired from active practice for 10 years before the truth dawned on me. I did indeed suffer from several physical ailments that are now known to be sometimes associated with autism, and it was these rather than the psychiatric symptoms that led to my failure to keep practicing beyond the usual retirement age.

Current trends make me question whether the neurotypical majority is correct in labeling us as abnormal and whether perhaps many of the more severe grades of autism might actually be

caused by the treatment we receive at the hands of that majority. Are you quite sure we are in fact abnormal? Could it just be that we are different?

J. Michael Hayman
Laurieton, Australia

DEFENDING D.A.R.E.

I read with interest "Just Say No?" by Scott O. Lilienfeld and Hal Arkowitz [Facts and Fictions in Mental Health]. After reading it, I couldn't help but wonder what value there was in writing such an article. Your criticisms were of a D.A.R.E. program that is no longer being administered. I'm sure you were unaware of that fact, otherwise I'm confident that you would have mentioned that the D.A.R.E. program that exists today (D.A.R.E. keepin' it REAL) is indeed evidence-based. It has been evaluated to be a good use of police resources and is very beneficial to kids.

In the interest of fairness to the story, you were also remiss in not mentioning that the previous D.A.R.E. program did include the peer role playing that you claimed it lacked.

I've been a D.A.R.E. officer for 15 years and have never taught a version of the program where the message is simply "just say no." D.A.R.E. has always given the students a variety of tools to help them make safe and responsible choices surrounding not only the use of substances but in most any circumstance. Perhaps even more valuable, but seldom regarded, is that the program affords an opportunity for the police to build healthy and mutually beneficial relationships with the schools, the kids and their families. To suggest that D.A.R.E. "doesn't work" indicates that your expectation was that the program should act as a "vaccination" against drug use. Although it would be great if such a thing actually existed, the fact remains that it doesn't.

It would be nice to see some support for the effort and not have reputable publications such as yours use outdated and misguided data as a means of promoting damaging misinformation.

Scott Hilderley
RCMP Drugs and Organized Crime Awareness Service
Victoria, B.C.

LILIENFELD AND ARKOWITZ REPLY:
Hilderley's assertions to the contrary, the older and ineffective D.A.R.E. program is still administered widely in school districts in the U.S. and other countries. As we also noted in our article, "the good news is that some proponents of D.A.R.E. are now heeding the negative research findings and incorporating potentially effective elements, such as role playing with peers, into the intervention." In fact, we did note that traditional D.A.R.E. programs sometimes afford opportunities for peer rehearsal but that these opportunities are insufficient. We also pointed out that there is reason for cautious optimism regarding revised D.A.R.E. programs.

Nevertheless, we do not share Hilderley's conclusion that the revised D.A.R.E. program is "evidence-based." As Renee Singh of the University of California, Santa Barbara, and her co-authors observed in a 2011 review, preliminary evidence suggests that this new program may exert promising effects on attitudes toward substance abuse and substance-refusal skills, but "empirical evidence to date does not provide compelling evidence of effectiveness" for this intervention.

CLIMATE CONTROL

As causes of violence, heat and cold are both stressors, as Ajai Raj and Andrea Anderson detailed in "Heat-Fueled Rage" and "Cold Confusion" [Head Lines]. The prefrontal cortex (PFC) is the part of the brain that makes us do the hard thing or, conversely, inhibits us from doing the easy thing. When there is an excess of stress, whether mental or physical, it is more difficult for the PFC to intervene and prevent automatic behavior. It is reasonable that thermal stressors would have a similar effect.

The lack of violence in cold weather is probably related to the fact that it is easier to stay warmer (and therefore mitigate stress) by staying inside. What would be interesting is whether domestic violence increases in cold weather, when the opportunity to take it out on someone else is lessened.

Pat King
Hot Springs, Ark.

ERRATUM

In "Heat-Fueled Rage," by Ajai Raj [Head Lines], the study by Solomon Hsiang and his colleagues is mistakenly cited as having appeared in *Nature*. The paper appeared in *Science* on September 13, 2013.

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Brain Science

Speaker: Larry Cahill, Ph.D.

Brains "R" Us

How do we work? What makes us tick? For much (but not all) of human history people looked to the gooey, grey organ between your ears for answers. Learn how how our perception of the brain has evolved and how some of our most "modern" ideas about the brain aren't very modern at all.

Sex on the Brain

Overwhelmingly, brain science has ignored gender differences with findings in males assumed to apply equally to females. But it turns out that "sex matters" down to the level of single neurons, even to parts of neurons. Find out why there are entrenched biases against sex difference research in brain science, and why they are, finally, crumbling.

Emotional Memory

What makes the brain a brain (and not a spleen or a pancreas or a lung) is memory, and emotion is arguably the primary sculptor of memory. Studies of emotional memory consequently lie at the heart of brain science. Explore the most dominant theories of emotional memory, and discover how sex matters (yet again) to these theories.

When Brains Fail

The brain is the single most complicated system in the known universe. When human brains fail, they can fail spectacularly, sometimes failing in fascinating ways that challenge some of our most elementary assumptions about who we are. What have we learned about the human brain from studying brain disease? Find out with Dr. Cahill.

Planets

Speaker: David Stevenson, Ph.D.

Planetary Diversity

The Kepler spacecraft has found hundreds of planets and thousands of additional candidates. Exploration of our solar system leads to a view of planets that emphasizes diversity rather than similarity. With so many planets out there, yes, some must be like Earth, but are the most exciting prospects for planets and life forms very different from our home? Absorb the possibilities.

Origin of Earth & Moon

Four and a half billion years ago our own solar system developed from a disk of gas and dust. Get our current understanding of this process and how Earth emerged with the Moon, an atmosphere, oceans, a magnetic field, and conditions for life. Explore how the nature of Earth is inextricably linked to the existence of our satellite companion.

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Ice Worlds
There is more ice and liquid than rock in our solar system, including some exotic stuff: hot, dense soups of protons and oxygen ions deep under planetary surfaces; rivers and lakes of liquid hydrocarbons, and ice geysers. Find out the details as we explore the structure and dynamics of the large satellites and Pluto.

Jupiter!
Our solar system's largest planet, Jupiter, likely influenced Earth's formation and so is a key to understanding Earth. Delve into Jupiter's internal properties and interior structure, and family of satellites. Get an insider's scoop on the billion dollar Juno mission arriving at Jupiter in July 2016 and learn about Dr. Stevenson's Juno role studying Jupiter's gravity and magnetic fields.

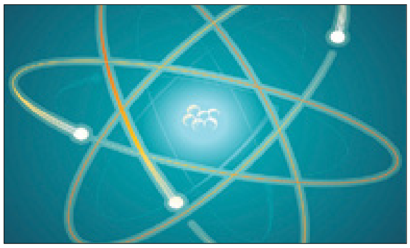
Weather
Speaker: Robert G. Fovell, Ph.D.

How and Why Clouds Form
Clouds are key in the planetary energy balance and water cycle. Historically, they have signaled atmospheric processes to observers. Learn about clouds' characteristics, formation, and function, with details on precipitation, ice, and lightning. We'll look at clouds from all sides, identifying the many ways clouds are essential to Earth and the atmosphere.

How and Why the Winds Blow
Delve into the role, causes and features of this invisible phenomenon. We'll look at the basics of atmospheric circulation and the complex interactions within the atmosphere that create wind. Learn about local winds (sea breezes), large-scale ones (fronts and cyclones) and legendary severe winds associated with mountains. Hone your knowledge of wind and its impacts.

Severe Storms
Storms impact our wellbeing, homes, cities, and economies. Learn about the causes, formation, and lifecycle of severe storms. Look at supercell thunderstorms and tornadoes, and the role of moisture and vertical wind shear in storms. From squall-lines, bow echoes, and flash flooding to hurricanes, get the latest need-to-know information on these forces of nature.

Understanding Extreme Weather
Synthesizing our knowledge from the three previous sessions, we'll apply these concepts to examples of extreme weather events from the recent past: 2013's devastating Colorado floods. The 2013 Oklahoma tornadoes. 2012's Hurricane Sandy. 1993's epic East Coast Snowstorm. 1991's "Perfect Storm."



Particle Physics
Speaker: James Gillies, Ph.D.

Hunting the Higgs Boson
Particle physics is the study of the smallest indivisible pieces of matter and the forces that act between them. Learn about the particle accelerators, detectors and computing that make this research possible at the Large Hadron Collider, and how hundreds of physicists teamed to hunt the long-sought Higgs boson.

Life after Higgs: What's Next?
Physicists at the Large Hadron Collider announced in 2012 they'd found *a* Higgs boson. But not *the* Higgs boson. What's the difference? Learn what the particular properties of the recently discovered particle could tell us about the nature of the universe, and why physicists don't know yet which Higgs boson they've found.

60 Years of Science for Peace
Sixty years ago, the idea of CERN, the European particle physics laboratory, was born. Hear the interwoven scientific and political stories of CERN's development and how particle physics has evolved from a regional to a global field, with the Large Hadron Collider as its frontier research tool.

Celebrating 25 years of the World Wide Web
"Vague, but exciting," were the words scrawled on Tim Berners-Lee's 1989 proposal for what became the World Wide Web. Hear the story of the Web's birth based on archival material and interviews with the major players, and learn how developments in physics and computing paralleled the development of the Web itself.

Astrobiology
Speaker: Peter Smith, Ph.D.

NASA's OSIRIS-Rex Mission
Learn about NASA's planned OSIRIS-REx mission to rendezvous with an asteroid and chip away samples to return home. Its target, the carbon-rich asteroid Bennu, should offer a peak at the types of organic materials and primitive minerals that existed on Earth when life was first forming.

The Earliest Life on Earth
Delve into the field of astrobiology, which investigates the origin of life on Earth and elsewhere. We'll probe the big questions: Was Earth seeded with life from space? Why is the backbone structure of DNA rarely found in nature? And what did the first microbes eat?

Life on Mars: What Do We Know?
Since the Viking missions of 1976, scientists have searched Mars for signs of life. From evidence of past water to questions of volcanism and methane gas, learn about the many signals that could tell us whether the Red Planet does, or ever did, host life.

Could Life Exist on Europa, Enceladus or Titan?
Some of the most intriguing potential sites for life in our solar system exist not on planets, but on moons with buried liquid oceans and lakes of methane and ethane full of organic materials. Learn why scientists are so interested in Saturn's moons Enceladus and Titan and Jupiter's moon Europa.

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Head Lines

INSIGHTS INTO THE SCIENCE OF YOU

Forward-Thinking Apes

M **NEWS FROM OUR WEB SITE** Environmental toxins and pollutants appear to increase the risk of developing Alzheimer's disease.

Animals, Deep in Thought Reasoning in the abstract is not for humans alone

CATEGORICALLY SMART

Several species can think conceptually about the things they see

Our knack for language helps us structure our thinking. Yet the ability to wax poetic about trinkets, tools or traits may not be necessary to think about them abstractly, as was once suspected. A growing body of evidence suggests nonhuman animals can group living and inanimate things based on less than obvious shared traits, raising questions about how creatures accomplish this task.

In a study published last fall in the journal *PeerJ*, for example, Oakland University psychology researcher Jennifer Vonk investigated how well four orangutans and a western lowland gorilla from the Toronto Zoo could pair photographs of animals from the same biological groups.

Vonk presented the apes with a touch-screen computer and got them to tap an image of an animal—for instance, a snake—on the screen. Then she showed each ape two side-by-side animal pictures: one from the same category as the animal in the original image and one from another—for example, images of a different reptile and a bird. When they correctly matched animal pairs, they received a treat such as nuts or dried fruit. When they got it wrong, they saw a black screen before beginning the next trial. After hundreds of such trials, Vonk found that all five apes could categorize other animals better than expected by chance (although some individuals were better at it than others). The researchers were impressed that the apes could learn to classify mammals of vastly different visual characteristics together—such as turtles and snakes—suggesting the apes had developed concepts for reptiles and other categories of animals based on something other than shared physical traits.

THINKSTOCK (*dogs*)

SMALL BRAINS, BIG IDEAS

Bees understand abstract relations despite lacking the brain areas thought necessary

In apes and humans, the prefrontal cortex is the seat of higher-order cognition, allowing us to reason about the world around us. Insect brains are much simpler and lack anything resembling a prefrontal cortex, yet a new study finds that honeybees can learn to differentiate between objects based on their relation to one another, such as "same or different" and "above or below."

Researchers at the University of Toulouse in France and their colleagues trained bees to enter a Y-shaped maze and travel down one of the arms to receive a reward. At the entrance to the maze, the bees were shown a simple image, such as a circle with black and white vertical stripes. At the fork, each possible path was marked with its own simple image: one path displayed the same vertical stripes, and the other path displayed horizontal stripes. Some bees were rewarded if they crawled down the arm of the maze that was marked with the same stripe pattern as the entrance; others learned to enter the arm that was marked with a different pattern.

After the bees had learned whether "same" or "different" marked the right path, the researchers changed things up—they presented the bees with a colored swatch at the opening to the maze instead of a stripe pattern. At the fork, one path was marked with the same color as the entrance, and the other path was marked with a different color—and the insects continued to choose the correct path, demonstrating that their understanding of same and different carried over to the new stimuli. Similar setups showed the bees could also master the concepts of above versus below and left versus right.

The findings offer insight into the evolution

PRECEDING PAGE: NICK GARBUTT *Getty Images*; ISTOCKPHOTO (*bee*)

M Keeping different sleep schedules on work days and days off, known as social jet lag, might be as disruptive as flying across time zones.

Dogs, too, seem to have better than expected abstract-thinking abilities. They can reliably recognize pictures of other dogs, regardless of breed, as a study in the July 2013 *Animal Cognition* showed. The results surprised scientists not only because dog breeds vary so widely in appearance but also because it had been unclear whether dogs could routinely identify fellow canines without the advantage of smell and other senses. Other studies have found feats of categorization by chimpanzees, bears and pigeons, adding up to a spate of recent research that suggests the ability to sort things abstractly is far more widespread than previously thought.

There is still some question as to whether such visual categorization experiments reflect truly abstract thinking by animals, says Vonk, who noted that further work is needed to untangle the tricks various animals use in classification challenges. "I suspect the different species use different means of solving the task," she notes.

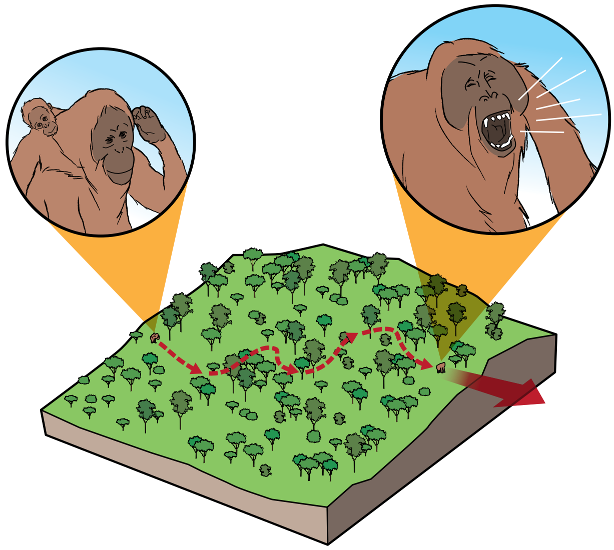
—*Andrea Anderson*

of intelligence. The bees' success suggests that this type of abstract cognition far predates the evolution of the large mammalian brain, according to Aurore Avarguès-Weber, a neuroscientist at Toulouse and co-author of the study published in October 2013 in *Proceedings of the Royal Society B*. Avarguès-Weber and co-author and colleague Martin Giurfa hypothesize that sociability and navigation skills may give rise to concept learning, which means the ability to think abstractly very likely exists in yet other species with nervous systems entirely unlike our own. —*Issa McKinnon*

JASON LEE (*orangutans*); THINKSTOCK (*animals*)

Orangutans, Check Your Schedules

The apes can draft a plan and communicate it with their troop



Very few animals have revealed an ability to consciously think about the future—behaviors such as storing food for the winter are often viewed as a function of instinct. Now a team of anthropologists at the University of Zurich has evidence that wild orangutans have the capacity to perceive the future, prepare for it and communicate those future plans to other orangutans.

The researchers observed 15 dominant male orangutans in Sumatra for several years. These males roam through immense swaths of dense jungle, emitting loud yells every couple of hours so that the females they mate with and protect can locate and follow them. The shouts also warn away any lesser males that might be in the vicinity. These vocalizations had been observed by primatologists before, but the new data reveal that the apes' last daily call, an especially long howl, is aimed in the direction they will travel in the morning—and the other apes take note. The females stop moving when they hear this special 80-second call, bed down for the night, and in the morning begin traveling in the direction indicated the evening before.

The scientists believe that the dominant apes are planning their route in advance and communicating it to other orangutans in the area. They acknowledge, however, that the dominant males might not intend their long calls to have such an effect on their followers. Karin Isler, a Zurich anthropologist who co-authored the study in *PLOS ONE* last fall, explains, "We don't know whether the apes are conscious. This planning does not have to be conscious. But it is also more and more difficult to argue that they [do not have] some sort of mind of their own." —*Isaac Bédard*

BRAINY BEASTS





❶ Capuchin monkeys appear to have a sense of fairness, insisting on receiving as good a food reward as their peers for performing the same job.

❷ Scrub jays can relocate food that has been hidden for months and may even remember how long it has been stored. The jays also anticipate potential thefts and will relocate their food if they think another jay has spotted it.

❸ Rhesus macaques will not pull a chain that brings them food if they think it will harm a fellow monkey.

❹ Male voles may be able to predict when a female will be most fertile and, at the opportune time, revisit the location where she was last seen.

❺ Bonobos and orangutans can use tools to retrieve food and then save their tools for later use.

In a recent survey, 87 percent of respondents said they would zap their brain with electricity if it could enhance their performance at school or work.

IS MEDITATION OVERRATED?

The scientific evidence is scant for many of the practice's widely touted benefits

Many people who meditate believe that the practice makes them healthier and happier, and a growing number of studies suggest the same. Yet some scientists have argued that much of this research has been poorly designed. To address this issue, Johns Hopkins University researchers carefully reviewed published clinical trials and found that although meditation seems to provide modest relief for anxiety, depression and pain, more high-quality work is needed before the effect of meditation on other ailments can be judged.

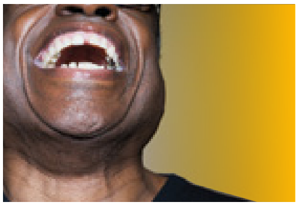
Madhav Goyal, an assistant professor of medicine at Johns Hopkins, and his colleagues identified 47 clinical trials published through 2012 that evaluated the effects of meditation on individuals with diagnosed health problems. They included only trials in which subjects were randomly assigned to a group that either meditated or participated in a control intervention, such as cognitive-behavior therapy or training to improve attention. More important, to make for a fair comparison, the control condition had to require a similar amount of time and focus as meditation did. Goyal and his colleagues also considered whether the researchers attending to the subjects knew what intervention they had received; ideally they should not, because this knowledge can influence how researchers interact with and assess subjects. Only 3 percent of meditation studies met these stringent criteria.

Describing their results in January in *JAMA Internal Medicine,* the researchers found moderate evidence that mindfulness meditation alleviates pain, anxiety and depression—the latter two to a similar degree as antidepressant drug therapy. Mindfulness meditation, the most widely researched approach, requires focusing one's attention on experiencing the present moment. The scientists did not have enough data to assess other common claims of its benefits, including that it improves mood or attention, or other forms of meditation, such as mantra-based practices.

Goyal argues the lackluster results simply reflect the fact that there is not enough evidence to reach other conclusions, in part because funds for high-quality meditation research are hard to come by. "That's part of the reason why the trials that we're seeing have relatively small sample sizes, and many of them have problems with their quality," he says. Plus, meditation may provide broad lifestyle benefits that go beyond treating disease and are thus difficult to measure. Allan Goroll, a professor of medicine at Harvard University, who published a commentary in the journal at the same time, hopes that the results—or lack thereof—"will be a stimulus for scientists to address these questions in a scientific way," he says. "We need to apply the scientific method to therapies both conventional and unconventional so we can find out what works." *—Melinda Wenner Moyer*

Orange You Glad I Didn't Say Banana?

Hints about the punch line of a joke or story may not spoil the fun



Hearing a punch line before the setup will predictably spoil a joke. But what of running gags and callbacks? Often a joke is *funnier* when it is familiar. An article published online in December 2013 in *Cognition and Emotion* resolves this paradox by applying research on insight.

Sascha Topolinski, a psychologist at the University of Cologne in Germany, studies processing fluency: when information is absorbed easily, it feels more true and beautiful. Repetition can increase fluency, which is why we prefer familiar music and art. Research also shows that "spoilers" do not always spoil. A 2011 paper in *Psychological Science* found that subjects who first read summaries of stories later enjoyed those tales more—even mysteries and stories with an ironic twist.

A sudden rise in fluency feels especially good, lending the experience of insight its pleasurable kick. In his studies, Topolinski presented subjects with 30 jokes. But first they saw 15 words—one word from half of the punch lines. Subjects found those 15 jokes funnier than the others. They could not predict the punch lines from the hints, which means the words did not spoil the jokes; they just made the punch lines quicker to process.

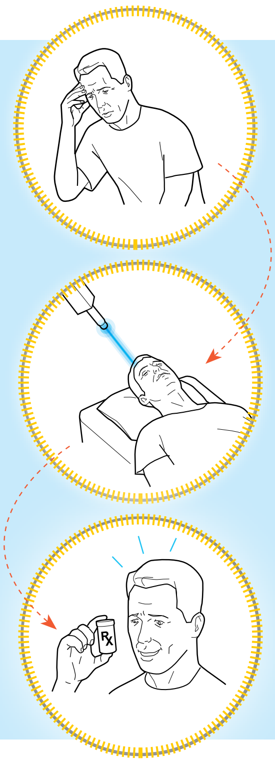
Humor is dynamic: "You first get this 'ugh' irritating moment, and then 'ah, I got it,'" Topolinski says. The more fluent the "I got it" moment, the funnier the joke—laughter depends on how fast the resolution pops into your head. In a final study, jokes seemed funnier when the punch line was written in an easy-to-read font. So when telling a joke, try hinting at the punch line before dropping the final bomb. You want your audience laughing, not pausing to scratch their heads. *—Matthew Hutson*

THINKSTOCK

M Physical activity and social engagement cause cells to dispatch tiny sacs of materials that serve as repair kits for the brain.

ON THE HORIZON

LASERS THAT DETECT NEUROLOGICAL DISEASE



When you suspect a fever, you pop a thermometer in your mouth and take your temperature. In diseases such as Alzheimer's and Parkinson's, no simple tool can identify its biological traces. Now hope is emerging from an unexpected source: lasers. A new study suggests that a laser technique thought to be safe in humans can identify the telltale protein clumps that accumulate in these disorders.

Amyloid fibrils, which are dense buildups of abnormally folded proteins, occur in many neurological diseases. Currently the only way to detect them in the brain is during a postmortem dissection or using highly expensive PET scans. The new study, published in the December 2013 issue of *Nature Photonics,* uses a method called Z-scan spectroscopy to examine amyloid fibrils. The proteins' unusual structure appears to cause them to absorb more light than healthy tissue, which means a laser could theoretically detect their presence. Yet these are early days; we do not yet know if other proteins in the body could interfere with detection, according to Piotr Hanczyc, a chemist at the Chalmers University of Technology in Sweden, who led the study.

The current experiment used fibrils suspended in quartz, so the next step will be to extend the technique to living tissue. If scientists can pull it off, this method could represent a major advance in the diagnosis of these diseases, according to Daofen Chen, a program director at the National Institute of Neurological Disorders and Stroke. "You could intervene earlier," Chen says. "That would provide a huge benefit."

—*Ajai Raj*

MY BRAIN MADE ME PULL THE TRIGGER

Neuroscience-based defenses are flooding the courtroom

The introduction of a brain scan in a legal case was once enough to generate local headlines. No more. Hundreds of legal opinions every year have begun to invoke the science of mind and brain to bolster legal arguments—references not only to brain scans but to a range of studies that show that areas such as the amygdala or the anterior cingulate cortex are implicated in this response or that. The legal establishment, in short, has begun a love affair with all things brain.

Nita Farahany, a professor of law at Duke University, laid out the extent of this infatuation at the 2013 meeting of the Society for Neuroscience. Helped by a team of 20 law students and undergraduates, her research sifted through a massive pool of data to find more than 1,500 judicial opinions from 2005 to 2012 in which an appellate judge mentioned neurological or behavioral genetics evidence that had been used as part of a defense in a criminal case. "The biggest claim people are making is: Please decrease my punishment because I was more impulsive than the next person, I was more likely to be aggressive than the next person, I had less control than the next person," Farahany said at a press conference.

Most neuroscientists think that studying brain scans may elicit overarching insights

In a trial in Smithland, Ky., a radiologist points to missing brain matter in a scan of a murderer's brain.

into the roots of violence, but individual scans lack the specificity to be used as evidence. "I believe that our behavior is a production of activity in our brain circuits," psychiatrist Steven Hyman of the Broad Institute in Cambridge, Mass., told a session at the American Association for the Advancement of Science's annual meeting earlier last year. "But I would never tell a parole board to decide whether to release somebody or hold on to somebody based on their brain scan as an individual, because I can't tell what are the causal factors in that individual."

It does not seem to matter, though, what academic experts believe about the advisability of brain scans at trial. Farahany found that most cases where neuroscience evidence was introduced resulted in an unfavorable outcome for the defendant, but not all. A bizarre twist has turned up in some cases in which a defendant overturned a decision that went the wrong way by accusing his counsel of failing to look into whether he had some kind of brain abnormality—ineffective counsel typically being an impossibly difficult claim. "If you were asleep as a defense counsel the entire time during the trial, if you were dead during the trial or if you failed to investigate a brain abnormality, you can be found responsible for ineffective assistance of counsel," Farahany said. "That's a surprising trio."

There is more to come. The arrival of brain science in the courtroom is "challenging fundamental concepts of responsibility and punishment," Farahany said. "Should we hold people responsible for their actions once we understand concepts of impulsivity?"

Brain science also has implications for the fate of a convicted offender. "This is a country largely focused on retributivism as a basis for punishment," she continued. "Is that a legitimate justification for punishment, or do we need to rethink what we do and instead focus more on rehabilitation?" Whichever way things go, jurors and judges are going to be hearing a lot more about amygdalae and orbitofrontal cortices.

—*Gary Stix*

JASON LEE (*cartoon*); ISTOCKPHOTO (*sun icon*); JOHN WRIGHT *AP Photo* (*courtroom*)

M Why are dogs so into us? According to one study, it boils down to their oxytocin receptor gene. | Child prodigies differ from regular kids not in their IQ but

THE CASE FOR MEDICAL MARIJUANA

New York is on track to become the 21st state to legalize medical marijuana this year, and two states—Colorado and Washington—have decriminalized recreational use as well. Americans now overwhelmingly support fewer restrictions on marijuana, with 86 percent saying doctors should be allowed to prescribe the drug for medical purposes.

Despite its surging popularity, the jury is still out on whether marijuana is truly the panacea its supporters claim it to be. Until recently, the drug's illegal status impeded rigorous study of its effectiveness. Several research groups are now taking advantage of today's looser laws to seek out answers. Here is where we stand for the six most studied conditions.

—Roni Jacobson

Cancer

Numerous trials have indicated that medical marijuana increases appetite and reduces chemotherapy-related nausea in the short term. Yet it may not be as effective as other recently developed drugs, so marijuana is not considered a first-line treatment for these symptoms.

Epilepsy

Multiple animal studies have suggested that THC, one of the main psychoactive chemicals in cannabis, may inhibit the brain processes thought to cause seizures. High-quality human studies are lacking, however, leaving many open questions.

Glaucoma

Several studies have found that smoking marijuana lowers pressure inside the eye, relieving glaucoma-related discomfort for about three to four hours. Yet a number of pharmaceutical drugs have been shown to be more effective and longer lasting than medical marijuana.

HIV/AIDS

In one randomized controlled trial, patients given a cannabislike compound were twice as likely to gain weight as patients given a placebo—a boon for people battling the wasting effects of this disease. The treatment's long-term effectiveness remains untested.

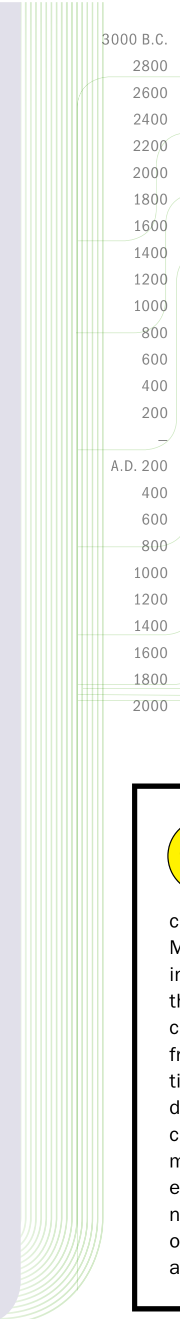
Multiple sclerosis (MS)

A large trial published in 2012 found that a cannabis extract significantly decreased muscle stiffness and other MS symptoms. A smaller study found that smoking cannabis worked better than a placebo in reducing both spasticity and pain in treatment-resistant participants. Given the few therapies available for MS, a 2011 review concluded that medical marijuana might be a viable way to manage certain symptoms.

Pain and inflammation

Studies have suggested that marijuana is only slightly better than a placebo in reducing acute inflammation, and it may even increase the perception of pain in some patients. When taken in combination with other medications, however, various cannabis-derived drugs have been shown to be moderately effective for reducing chronic neuropathic pain.

MEDICAL MARIJUANA'S DEEP ROOTS



2700 B.C.: Legendary Chinese emperor Shennong is said to discover the healing properties of marijuana.

1500: Medical papyri from Egypt mention marijuana as a cure for sore eyes and inflammation.

600: Bhang, a drink of cannabis and milk, is used widely as an anesthetic in India.

A.D.79: Roman naturalist Pliny the Elder cites boiled cannabis roots as a treatment for gout, pain and cramped joints.

800: Islamic physicians prescribe cannabis for a variety of ailments, although some decry it as a "lethal poison."

1542: German physician Leonhart Fuchs names the plant *Cannabis sativa*.

1842: British army surgeon William Brooke O'Shaughnessy introduces marijuana into medical practice as a treatment for pain, nausea and convulsions.

1850: The United States Pharmacopeia, which issues the official handbook for dispensing medications, classifies marijuana as a legitimate medical compound.

1925: A League of Nations treaty limits cannabis use to medical or scientific purposes. Aspirin and other newly developed drugs begin to replace cannabis as treatments for pain.

1930: Harry J. Anslinger is appointed commissioner of the Federal Bureau of Narcotics. He considers marijuana a corrupting influence and helps to turn public opinion against the drug.

HAPPIER DAYS

Although clear evidence for medical marijuana is lacking for many ailments, it is important to note that these clinical results do not consider improvements in overall quality of life. Many users report improved mood and decreased anxiety and insomnia as invaluable benefits of the drug. Furthermore, some of the pharmaceutical treatments that have outperformed marijuana come with unpleasant side effects. Consider Megestrol, a drug frequently given to people with cancer or AIDS to increase appetite. It encourages more sustainable weight gain than marijuana does but has the distressing side effect of impotence. For taxing conditions with few treatments, such as MS, medical marijuana may be the only way to provide relief for patients who have exhausted conventional therapies. So although most doctors do not recommend medical marijuana as a first-line treatment, they often prescribe it either in combination with other medications or as an alternative for patients with a low tolerance for side effects.

ISTOCKPHOTO (*pills icon*); GETTY IMAGES (*marijuana leaves*)

in their astounding working memory. | Asian elephants will console a distressed fellow elephant by touching the other animal with their trunk and chirping.

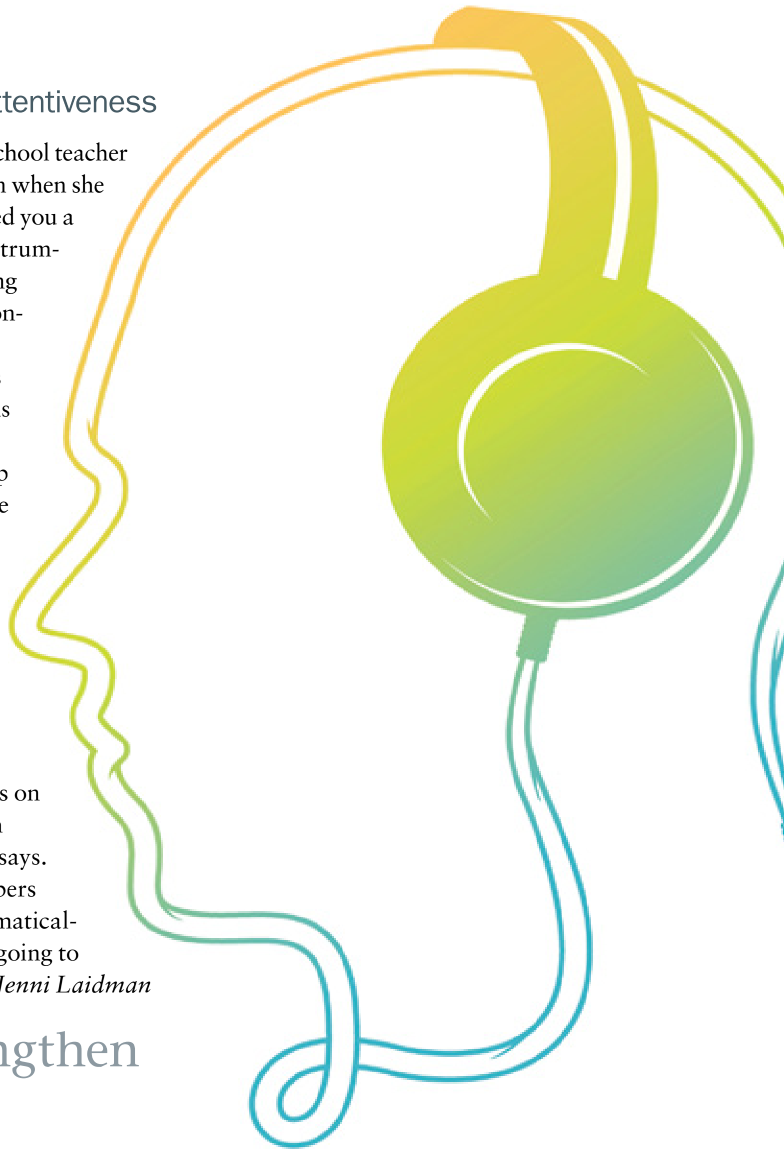
Melody as Remedy How music eases our pain and improves our mental fitness

MUSIC HELPS KIDS READ

Making music improves auditory precision and attentiveness

She probably didn't realize it, but your preschool teacher very likely provided your first reading lesson when she cranked up "Yellow Submarine" and handed you a noisemaker. Today a symphony of research trumpets the many links among language, reading and music, including several that reveal a connection between rhythm and reading skills. Nina Kraus of Northwestern University has discovered a possible explanation: the brains of good beat keepers respond to speech more consistently than the brains of people whose toes do not tap in time. After testing 124 adolescents for beat-keeping ability, the researchers used an electroencephalogram (EEG) to eavesdrop on teen brains as the consonant sound "da" was played repeatedly. With every "da," the brains of beat keepers responded consistently, even when there was background noise or while they watched television. The brain waves of poor beat keepers, however, were all over the place.

The study helps to explain why music may hold a key to improved reading. Because reading ability, in general, relies on making a connection between the sounds of letters and symbols on a page, music provides another avenue into learning. "Through music, you learn to pay attention to important sounds," Kraus says. The inconsistent sound processing shown by the poor beat keepers makes that difficult. "If you have an auditory system that automatically is able to efficiently pull out sounds that are meaningful, it's going to be important not just for music but for speech." —*Jenni Laidman*



Pick up an instrument to strengthen reading and listening skills.

FIGHTING POVERTY WITH PIANOS

Music lessons may help close the socioeconomic gap in reading ability

Scientists have observed that reading ability scales with socioeconomic status. Yet music might help close the gap, according to Nina Kraus and her colleagues at Northwestern University.

Kraus's team tested the auditory abilities of teenagers aged 14 or 15, grouped by socioeconomic status (as indexed by their mother's level of education, a commonly used surrogate measure). The researchers recorded the kids' brain waves with EEG as they listened to a repeated syllable against soft background sound and when they heard nothing. They found that children of mothers with a lower education had noisier, weaker and more variable neural activity in response to sound and greater activity in the absence of sound. The children also scored lower on tests of reading and working memory.

Kraus thinks music training is worth investigating as a possible intervention for such auditory deficits. The brains of trained musicians differ from nonmusicians, and they also enjoy a range of auditory advantages, including better speech perception in noise, according to research from Kraus's laboratory. The researchers admit that this finding could be the result of preexisting differences that predispose some people to choose music as a career or hobby, but they point out that some experimental studies show that musical training, whether via one-on-one lessons or in group sessions, enhances people's response to speech.

Most recently Kraus's group has shown that these effects may last. Kraus surveyed 44 adults aged 55 to 76 and found that four or more years of musical training in childhood was linked to faster neural responses to speech, even for the older adults who had not picked up an instrument for more than 40 years. —*Simon Makin*

GETTY IMAGES

M Not all happy lives are meaningful: researchers suspect happiness is about getting what we want, but meaningfulness is rooted in giving, effort and

Soothe physical discomfort by listening to ambient music.

PRESTO PAIN RELIEF

Soothing music helps patients heal after an operation

Forget stickers and popsicles—hospitals may soon begin handing their patients MP3 players to speed their recovery. A study at Our Lady of the Lake Regional Medical Center in Baton Rouge determined that ambient music therapy had a positive effect on postoperative patients' recovery by improving pain management and decreasing the negative effects of environmental noise.

In this study, patients who had undergone surgery for cancer all received standard nursing care. Half of them also got a preprogrammed MP3 player with ambient music—songs without words, played at less than 60 decibels—and were encouraged by nurses to listen for at least half an hour after they took their twice-daily medication. Before treatment, all the patients had similar levels of anxiety, pain and irritation at the amount of environmental noise. Three days later patients who listened to the ambient music said they were able to better manage their pain and were less annoyed by hospital noise, whereas patients without music experienced no change, according to the study in *Nursing* last fall. Most of us already turn to music to help with emotional pain; these findings suggest we might want to try listening as a salve for physical pain, too.

—Michaela Slinger

Sing Your Way to Fitness

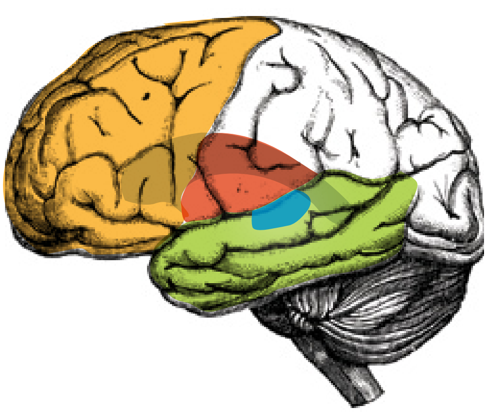
Producing tunes instead of simply listening may make your body more efficient

Chain-gang chants, military cadences, sea shanties: humans have long paired music making with intense physical exercise. Now research confirms the power of the combination: working out seems easier while producing music, according to a small study published in the *Proceedings of the National Academy of Sciences USA*.

In the study, half of the participants made music while working out by using software that turned their movements into tunes. These exercisers exerted equal force while pumping iron as did people who merely listened to music during exercise. Yet the music makers used less oxygen during their routine—a measure of exertion—and they also felt they were working less hard than those who just listened.

Music production may make exercise easier by activating so-called emotional motor control, posits Thomas Fritz, a postdoctoral fellow at the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig and the study's lead researcher. Emotional motor control is responsible for spontaneous actions such as a genuine smile; deliberate motor control, in contrast, implements purposeful action (such as a fake smile). Activating this more efficient system, Fritz says, may be as easy as singing along or pumping iron in rhythm with the tunes in your exercise playlist. *—Allison Bond*

Hum along with your playlist to get more out of a workout.



GETTY IMAGES (*jogger*); ISTOCKPHOTO (*brain*)

Music and Language, Intertwined

The brain activity for music and language is enormously complicated, and researchers are still trying to determine how the brain handles each process. Below is a sampling of what we do know: Areas in the **frontal lobe** (*orange*) help us learn the rules that govern language and music, such as those for syntax and harmony. Regions in the **temporal lobe** (*green*) help us perceive and understand sounds, such as the meaning of words and melodies.

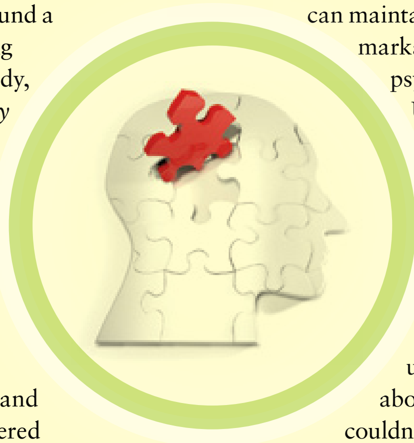
The **auditory cortex** (*blue*) appears to have distinct music and language roles: the left auditory cortex is important for decoding and discriminating different aspects of speech, whereas the right auditory cortex is more involved in perceiving the pitch and frequency of sound. The **insula** (*red*) processes rhythm, perhaps in subtly different ways, for both music and speech. And the **corpus callosum** (*gray*) is larger in the brains of musicians, suggesting that musicians require greater communication between the two hemispheres.

sacrifice. | Prions, the proteins made famous for their role in mad cow disease, also become active when your brain forms a long-term memory.

BREAKING BAD MEMORIES

Researchers selectively erase drug-related associations in rats

Cravings—we all have them. These intense desires can be triggered by a place, a smell, even a picture. For recovering drug addicts, such memory associations can increase vulnerability to relapse. Now researchers at the Florida campus of the Scripps Research Institute have found a chemical that prevents rats from recalling their drug-associated memories. The study, published online in *Biological Psychiatry* last fall, is also the first of its kind to disrupt memories without requiring active recollection.



Over the course of six days the rats in this study alternated between one of two chambers. On days one, three and five, the animals were injected with methamphetamine hydrochloride—the street drug known as meth—and placed in one room. On the even-numbered days they received a saline placebo and entered a different chamber.

After two more days, half the rodents were given a choice between the rooms. As expected, they showed a clear preference for the place they visited after receiving meth. The other half of the animals were injected with a solution containing Latrunculin A (LatA). This chemical interferes with actin, a protein known to be involved in memory formation. These animals showed no preference between rooms, even up to a day later: their choices seemed not to be driven by a memory of meth.

Previous research has suggested that drugs of abuse alter the way actin functions, causing it to constantly refresh memories associated with these drugs rather than tucking them away into typical memory storage, which is more inert. As a result of their active status, drug memories might remain susceptible to disruption long after their initial formation.

The idea that drug memories might differ in this way is relatively new, so the researchers double-checked this understanding by testing whether LatA could affect food associations. The rats underwent a similar regimen to create a mental link between food and environment. LatA injections had no effect on the animals' reactions to the different chambers, meaning it left the food associations intact.

"The claim that you have an active [actin process] that can maintain the memory days later is really remarkable," says Gary Lynch, a professor of psychiatry and human behavior at the University of California, Irvine. The next step is to find out what other types of memories—if any—share this property, so that we know exactly what kinds of recall this treatment can target, he says.

Courtney Miller, a co-author of the study and a neurobiologist at Scripps, points out that the technique's limited usefulness helps to alleviate ethical concerns about memory alteration. "You actually couldn't take our discovery and erase a run-of-the-mill memory in the brain, because it simply doesn't work. You can only actually get rid of these drug-associated memories." Miller emphasizes that the idea behind this research is to give those affected by drug addiction "a fighting chance to stay clean." *—Janali Gustafson*

MEDDLING WITH MEMORY

Researchers tinkered with recall in a spate of recent studies

1. Psychologists at Northwestern University showed that each time you recall an event, your brain alters the memory by integrating new information—perhaps drawing on your current mood, activity or location, among other things.

2. The moment of recall can also impair a memory, according to work at Iowa State University. Study participants watched an episode of the television show *24,* in which a terrorist used a needle during an attack. Some subjects were quizzed on the plot before they all listened to a recap that incorrectly said the weapon was a stun gun. Only the people who recalled a needle during the quiz had trouble remembering the weapon later.

3. Neuroscientists at the Massachusetts Institute of Technology implanted false memories in mice. The rodents first learned that one chamber was safe but that another was not—in it, they received an electric shock. When the mice later occupied the unsafe chamber, the scientists activated the memory of the safe room using an optical probe. The next day, when the rodents again entered the safe chamber, they froze in place—a sign of fear—even though they had never been shocked there.

4. A recent study at Emory University showed it might be possible to inherit memories from our parents and perhaps even our grandparents. Researchers trained mice to shudder in fear in response to a specific smell. The children and grandchildren of these mice displayed the same reaction to the odor, despite having never come across it before.

5. A jolt of caffeine, equivalent to about 12 ounces of coffee, made study subjects at Johns Hopkins University more likely to recall information they had just learned—but the effect may work only on people who do not drink caffeine regularly. *—Victoria Stern*

ISTOCKPHOTO

M To develop a child's social reasoning skills, try to pepper your speech with "thought words" such as know, forget, think and understand.

SEEING WITH THE BRAIN (NOT THE EYES)

The Spelunker's Illusion

Why some people believe they can see their hands in total darkness

Many people swear by the so-called spelunker's illusion, in which they think they can see their own hands moving even in the total absence of light. You don't have to see it to believe it: in a recent article in *Psychological Science,* cognitive scientists based at Vanderbilt University and the University of Rochester have demonstrated that this spooky illusion is real, and some individuals are more prone to these visions than others.

Through a series of five experiments, the researchers asked their 129 subjects to report visual sensation in total darkness. In the first four setups, subjects wore a blindfold to block all light. A subset of these participants claimed to see movement when they waved their own hand in front of their face but not when an experimenter waved his hand.

Why would only some people think they could see the motion? On the hunch that this illusion was created by intense connectivity among brain regions, the research team had included volunteers with a form of synesthesia, in which heightened brain connectivity causes letters and numbers to appear as certain colors. These subjects, they discovered, had even stronger visual reactions to their own hands moving in the darkness than did the other subjects.

Finally, the researchers decided to try out the experiment using eye-tracking headgear, again in complete darkness. The eye tracker revealed that the more vividly a subject reported seeing his or her own hand's motion, the smoother the eye movements were. That is, their eyes behaved as though they really could "see" and were locking onto an imaginary target. In reality the participant was anticipating the visual experience of his or her hand in space.

Taken together, the studies suggest that people with heightened connectivity between the senses possess a greater awareness of the body. The findings are also a reminder that "sight" is generated by your brain, not your eyes. "The brain may or may not use information your eyes provide," says Rochester cognitive scientist Duje Tadin. Instead your brain uses the eyes' information selectively alongside familiar or predictable patterns—such as your hands' movements—to construct what you ultimately perceive. *—Daisy Yuhas*

CHRIS GRAMLY *Getty Images* (*woman*); ISTOCKPHOTO (*eyes*)

> Dream visions may originate from random activity in the visual centers in the brain or in regions that store memories, which connect to visual areas.

The Man Who Could (Not) See Faces In one famous case study, a man who was completely blind could distinguish among photographs of happy and angry faces at a rate better than chance. Scientists learned that visual information was reaching his amygdala, a region that processes potential threats. Activity in his amygdala increased in response to faces that were gazing directly at him. When asked, he could not guess which pictures contained direct or averted gazes—yet his amygdala appeared to register which was which. *—V.S.*

NO VISION NECESSARY TO "SEE" LIGHT

Light triggers a quick neural reaction even in blind people

The presence of light may do more for us than merely allow for sight. A study by Gilles Vandewalle and his colleagues at the University of Montreal suggests that light affects important brain functions—even in the absence of vision.

Previous studies have found that certain photoreceptor cells located in the retina can detect light even in people who do not have the ability to see. Yet most studies suggested that at least 30 minutes of light exposure is needed to significantly affect cognition via these nonvisual pathways. Vandewalle's study, which involved three completely blind participants, found that just a few seconds of light altered brain activity, as long as the brain was engaged in active processing rather than at rest.

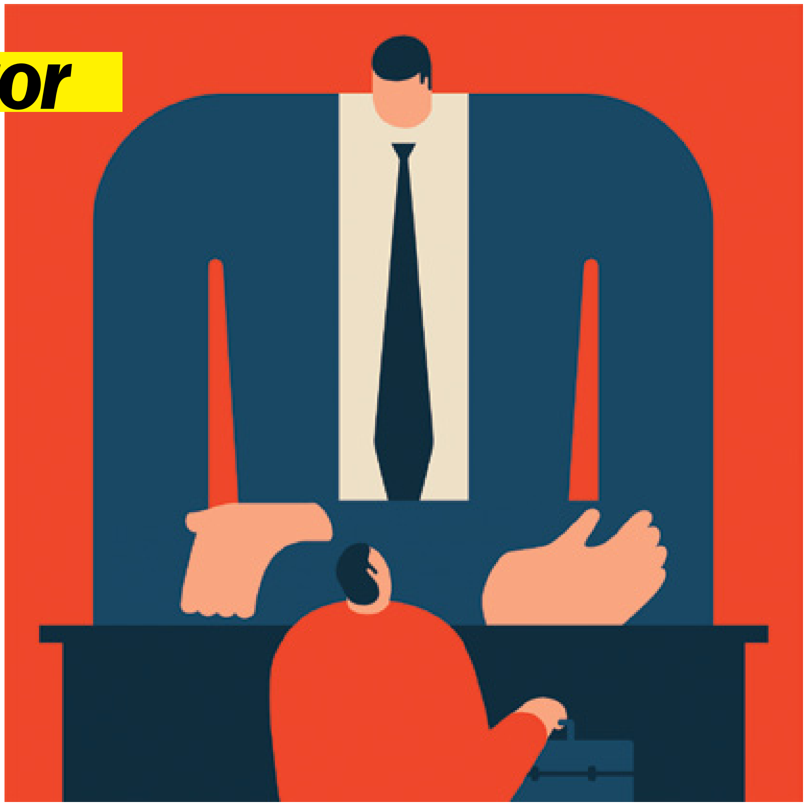
First the experimenters asked their blind subjects whether a blue light was on or off, and the subjects answered correctly at a rate significantly higher than random chance—even though they confirmed they had no conscious perception of the light. Using functional MRI, the researchers then determined that less than a minute of blue light exposure triggered changes in activity in regions of their brain associated with alertness and executive function. Finally, the scientists found that if the subjects received simultaneous auditory stimulation, a mere two seconds of blue light was enough to modify brain activity. The researchers think the noise engaged active sensory processing, which allowed the brain to respond to the light much more quickly than in previous studies when subjects rested while being exposed to light.

The results confirm that the brain can detect light in the absence of working vision. They also suggest that light can quickly alter brain activity through pathways unrelated to sight. The researchers posit that this nonvisual light sensing may aid in regulating many aspects of human brain function, including sleep/wake cycles and threat detection. *—Ariel Van Brummelen*

Brain scans can predict a child's future working memory, a capacity similar to a mental scratch pad, which in turn predicts academic success.

A GUIDE TO MASTERING YOUR WORLD

How to Be a Better *negotiator*



In my first experience with negotiation, a human resources rep at a publishing company offered me $24,000 a year for an entry-level gig. Having been coached never to take a first offer, I responded, "Is there any way you can do better?" A day later I was ecstatic to accept her second offer of $24,500. The victory, however small, set me up to be willing to negotiate the next time an opportunity arose. "I don't think it makes any difference if you're negotiating for the release of a hostage or trying to get a better price on a used car, the principles of being an effective negotiator are the same," says Russell Korobkin, a law professor at the University of California, Los Angeles, and author of a leading law school textbook, *Negotiation: Theory and Strategy,* 2nd edition (Wolters Kluwer Law and Business, 2009). Here are three research-proven ways to boost your negotiation game:

#1 Be fair. "Good negotiators should always think about how they can show the proposal they're making is fair to both parties," Korobkin says. "Fairness" does not have one exact definition, but social psychology studies suggest that an offer people consider fair is one that is similar to what other people in the same situation are getting, consistent with market prices or terms, or on par with a similar transaction you have made in the past. "If the deal is fair," he adds, "the person you're negotiating with never has to feel like they're being taken advantage of, and it'll make it easier for him to say yes."

#2 Strike a power pose. Psychologists have found that expansive, open postures ("high-power poses") make people feel more powerful and confident during stressful situations such as interviews or negotiations, whereas closed, curled-in positions ("low-power poses") do the opposite. One study by Harvard Business School social psychologist Amy Cuddy even found that striking high-power poses—such as elbows wide with hands on hips (think Wonder Woman), elbows wide with hands behind the head (think guy watching football), or leaning forward with arms wide, palms on a table (think leading a meeting)—causes an increase in testosterone and decrease in the stress hormone cortisol. In other research, Cuddy and her colleagues had student volunteers assume either a high- or low-power pose for seven minutes before giving a speech. Although the students stood normally during the speech, observers still found the high-power group more persuasive and said they would be more likely to hire them during a job interview.

#3 Aim high. Really high. Business research shows that people with more aggressive (but still realistic) goals—say, getting a 20 percent raise at work versus a 5 percent bump—end up doing better in negotiations. "One big reason for that is that people who have more aggressive goals make more aggressive first offers," Korobkin says. "Where you start has a lot to do with where you end up." This is called the "anchoring effect," a tried-and-true bit of business strategy that was first identified by psychologists Amos Tversky and Daniel Kahneman in the 1970s. Let's say you make $50,000 a year and want a raise—if you go into your boss's office with a target of $60,000 versus $52,000, you're going to make a higher first demand. That first number will influence the way your boss thinks as the negotiation proceeds, anchoring the back-and-forth. "If you ask for 75K, your boss may say, 'No way,' but in the subconscious part of her mind, she's trying to figure out what would be fair. Maybe 58 or 59 or even 60 might sound about right," Korobkin says. You still may not end up at your target figure, but by aiming high—within reason—you at least have a chance.

As much as it makes me break out in a cold sweat thinking about it, I am vowing to try out this last bit of advice during my next negotiation, which will likely be at a flea market or furniture shop because we are doing some redecorating. You're asking $125 for that midcentury modern end table? "I'll give you $75," I'll say. And then maybe I'll get it for what I really wanted to pay all along: something in between. *—Sunny Sea Gold*

PAUL PANTAZESCU iStockphoto (globe icon); MÁGOZ (illustration)

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In Plain Sight

Hidden illusions are the Easter eggs of the mind

He never once thought it probable, or possible, that the Minister had deposited the letter immediately beneath the nose of the whole world, by way of best preventing any portion of that world from perceiving it.

—Edgar Allan Poe, "The Purloined Letter," 1844

Sherlock Holmes's predecessor and Arthur Conan Doyle's inspiration, detective C. Auguste Dupin, conjured by Poe, used his powers of ratiocination to retrieve a stolen letter after two exhaustive police searches had failed. The police's mistake lay in hunting for intricate hideouts: secret drawers, excavated table legs, the insides of cushions. Too obvious, clearly. When the searches bore no fruit, the officers concluded that, contrary to their assumption, the letter must not be on the premises. But Dupin knew better: the police had missed the letter not because it was hidden too well but because it was lying in plain sight.

Our visual system's search strategies depend not only on what we are trying to find but also on our expectations and experience. False assumptions about size, shape or general appearance will hamper our examination, as will an abundance of potential search targets, a perceptual phenomenon called crowding. The authors of this column are frequent victims of the latter, especially at our unkempt desks, where we have been known to spend seemingly limitless time looking for letters—and many other documents—that were hiding in plain sight. The illusions we present here play hide-and-seek with your perception. Enjoy the hunt. **M**

MISSING THE FACE FOR THE TREE

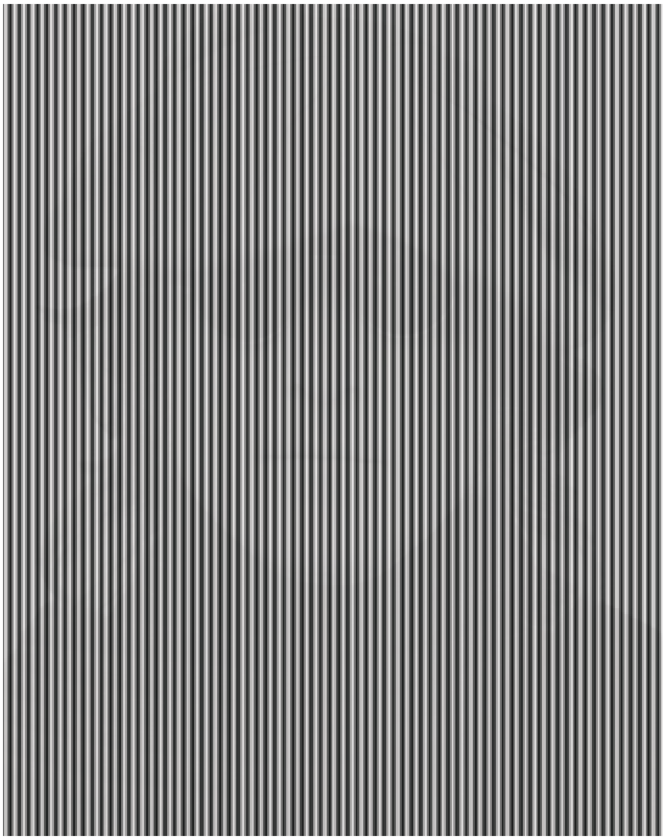
Mexican artist Octavio Ocampo's "metamorphic" paintings are rarely what they seem at first sight. Can you see the portrait of a young woman in this image? Step away from your computer screen, or hold your magazine at arm's length to see the three flying birds become delicate facial features. Our visual and oculomotor systems focus preferentially on objects rather than non-objects within a scene. This scanning bias allows the artist to hide the woman's likeness in plain view. When we focus on the birds flying in the foreground, we tend to ignore the facial contour in the background.

BY STEPHEN L. MACKNIK AND SUSANA MARTINEZ-CONDE

Stephen L. Macknik and Susana Martinez-Conde are laboratory directors at the Barrow Neurological Institute in Phoenix. They serve on *Scientific American Mind*'s board of advisers. Their book *Sleights of Mind,* with Sandra Blakeslee, won the 2013 Prisma Prize for Best Book of the Year (http://sleightsofmind.com). Their new book, *Champions of Illusion,* will be published by Scientific American/Farrar, Straus and Giroux.

Send suggestions for column topics to ***editors@SciAmMind.com***

OCTAVIO OCAMPO *Visions Fine Art (Family of Birds)*; SEAN McCABE *(Macknik and Martinez-Conde)*



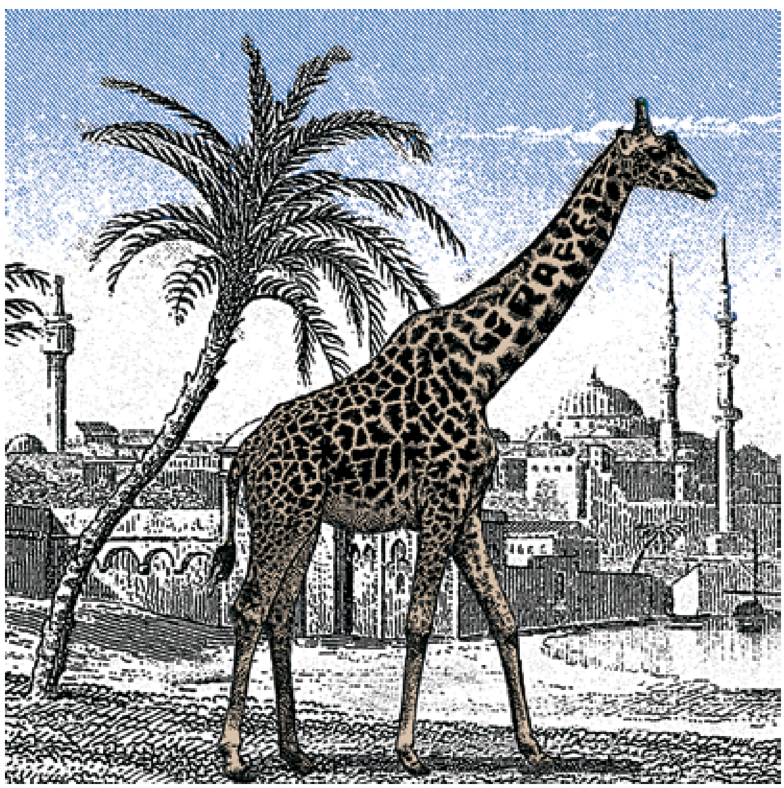
IMAGINE

You may say I'm a dreamer, but I can see John Lennon's face behind this grid of vertical bars. I wonder if you can. You can reveal Lennon's portrait in many different ways: squint your eyes, step away from the image, or look at the grid while shaking your head left and right vigorously, as if saying "no." It's easy if you try. The illusion, created by a composite of Lennon's portrait and a vertical black-and-white grid, works because under normal viewing conditions, your visual system's neurons respond maximally to the high-contrast vertical bars that are presented with high frequency across space, which obliterates the more subtle features of the portrait.

Want more? Follow these instructions to create similar illusions with your own photographs: **www.instructables.com/id/Hidden-Photo-Optical-Illusion**

THE VANISHING GIRAFFE

Magician and escape artist Harry Houdini had several signature tricks; one was to vanish a five-ton, eight-foot-tall elephant in front of thousands of spectators at the New York Hippodrome Theater, which he did in 1918. Naturally, it was an illusion. As is the vanishing giraffe in this image, created by artist Gianni A. Sarcone. Can you see the second giraffe in the scene? It may take you a while if you do not know what you are looking for. Our search strategy relies heavily on having a specific target in mind. If you are looking for a large object, you may miss smaller ones, and vice versa. And if you are looking for a picture, you may miss a critical word.

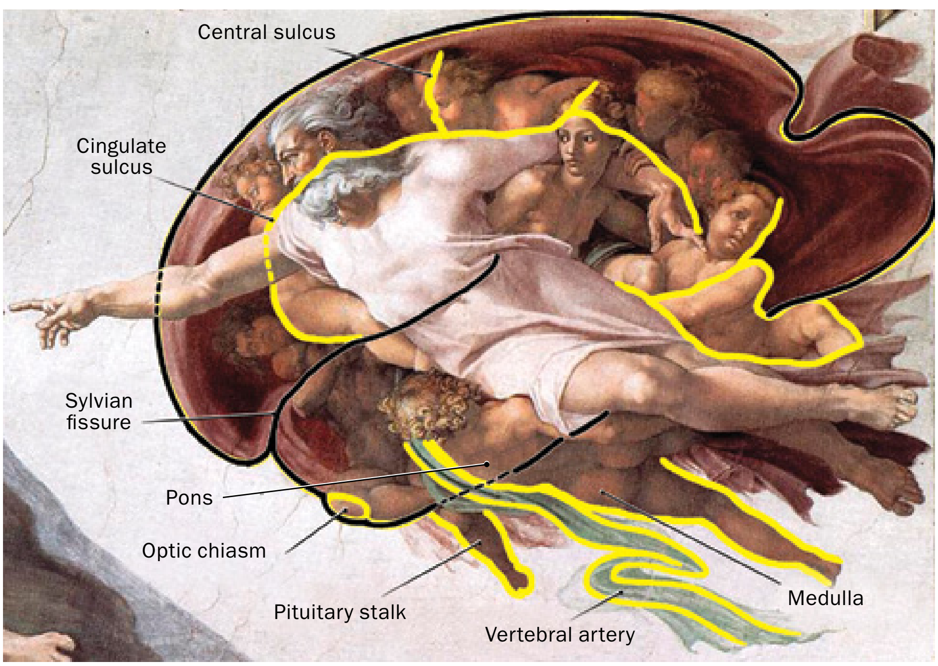


THE AMBASSADORS

This 1533 painting by German artist Hans Holbein the Younger features a legendary artistic Easter egg: a large skull centered at the bottom of the scene. The skull is painted in anamorphic perspective, so it is apparent only to viewers who observe the painting from the side but not to those who look at it from the front. The skull is a vanitas, from the Latin for "vanity," a reminder of our mortality, but the meaning of its prominent placement in the tableau and anamorphic perspective is still debated, as is the significance and symbolic connotation of the other objects in the room. Holbein's composition may incorporate a heavenly plane in the upper part of the painting—indicated by objects such as a crucifix, a celestial globe and a sundial—and an earthly plane in the lower part—symbolized by elements such as a terrestrial globe, books and the anamorphic skull.

IN THE BEGINNING WAS THE BRAIN

Michelangelo Buonarroti (1475–1564) was not only a magnificent painter and sculptor but also a master anatomist who conducted numerous dissections of human cadavers. Frank L. Meshberger of St. John's Medical Center in Anderson, Ind., and Ian Suk and Rafael J. Tamargo of the Johns Hopkins University School of Medicine have proposed that Michelangelo's Sistine Chapel frescoes conceal a variety of neuroanatomical structures. Meshberger's theory that *The Creation of Adam* hides an image of the full brain, possibly to portray God's gift of intellect to Adam, has gained support from art historians. More recently, Suk and Tamargo have put forward that *Separation of Light from Darkness,* one of the last frescoes that Michelangelo painted in the chapel, which depicts God's first act of creation, contains a view of the brain stem. They believe that the concealed anatomical features are not accidental but instead represent Michelangelo's wish, as a deeply religious man and accomplished anatomist, to enhance his depiction of God with his neuroanatomical knowledge. So it could be a matter of faith.



NATIONAL GALLERY, LONDON *Art Resource, NY* (The Ambassadors and *skull inset*); "CONCEALED NEUROANATOMY IN MICHELANGELO'S *SEPARATION OF LIGHT FROM DARKNESS IN THE SISTINE CHAPEL,*" BY IAN SUK AND RAFAEL TAMARGO, IN *NEUROSURGERY,* VOL. 66, NO. 5; MAY 2010

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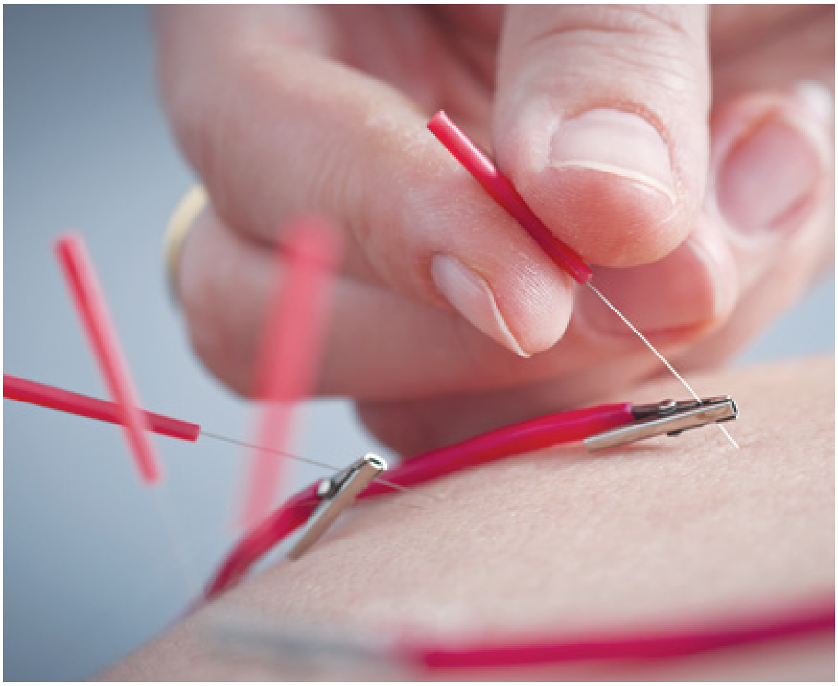

GETTY IMAGES

NERVOUS SYSTEM

Can Acupuncture Curb Killer Immune Reactions?

A needle-based technique has been shown to switch on nerves that tamp down sepsis

By Gary Stix

The ST36 Zusanli (足三里) acupuncture point is located just below the knee joint. This spot in mice—and it is hoped perhaps in humans—may be a critical entryway to gaining control over the often fatal inflammatory reactions that accompany systemic infections. Sepsis kills as many as 250,000 patients in the U.S. every year, some 9 percent of overall deaths. Antibiotics can control sepsis-related infection, but no current drugs have FDA approval for counteracting the runaway immune response.

Researchers at Rutgers University New Jersey Medical School reported online in *Nature Medicine* on February 23 that stimulating ST36 Zusanli with an electric current passed through an acupuncture needle activated two nerve tracts in mice that led to the production of a biochemical that quieted a sepsislike inflammatory reaction induced in mice. (*Scientific American Mind* is part of Nature Publishing Group.)

The finding, which also involved the collaboration of the National Medical Center Siglo XXI in Mexico City and other institutions, raises the possibility that knowledge derived from alternative medicine may provide a means of discovering new nerve pathways that can regulate a variety of immune disorders, from rheumatoid arthritis to Crohn's disease. If future studies achieve similar results, acupuncture might be integrated into the nascent field of bioelectronics medicine—also called electroceuticals—that is generating intense interest among both academics and drug companies.

Clues from Acupuncture

Luis Ulloa, who headed the study at the Center for Immunity and Inflammation at Rutgers, has spent more than 10 years researching how nerve signals control immune function. Following the suggestion of a Mexican colleague, he realized that it might be worth testing whether acupuncture could help discover some of these much sought neuroimmune pathways.

Ulloa and his team used electroacupuncture to stimulate the ST36 Zusanli acupuncture point in 20 mice exposed to lipids and carbohydrates from the outer membrane of bacteria, producing an inflammatory response that mimics sepsis. Another 20 rodents received "sham" electroacupuncture in which nonacupuncture points were stimulated. Half of the mice in the first group survived, whereas all the sham-treated rodents perished. A similar survival difference was noted with two groups of mice exposed to a cocktail of microbes in the gut.

Researchers then began to analyze the nerves and organs involved. They traced a pathway beginning in a branch of the sciatic nerve, not far from ST36 Zusanli, that relayed a signal to the spinal cord and then the brain. Once processed there, it was sent down to the vagus nerve, finally reaching the adrenal glands, which produced the key anti-inflammatory agent, the neurotransmitter

GARY STIX is a senior editor at *Scientific American* who covers neuroscience.

Send suggestions for column topics to **editors@SciAmMind.com** dopamine. Ulloa's team set about confirming the parts of this biological wiring diagram by removing independently sections of the key nerves and the entire adrenal glands. Excision of any one of these links in this newly discovered neuroimmune circuit abolished electroacupuncture's anti-inflammatory effects.

The researchers also succeeded in quelling inflammation by using a drug called fenoldopam (Corlopam), which acted as a stand-in for the adrenal-produced dopamine in mice who had the glands surgically removed. Having a drug at hand might be essential because the adrenals in many sepsis patients function poorly, which makes them unsuitable candidates for acupuncture therapy.

The Rutgers work with acupuncture might be a relatively noninvasive means of performing neuroimmune stimulation and researching the interaction between the nervous and immune systems. "There are hundreds of these [neuroimmune] circuits that haven't been mapped, and some of them may map to acupuncture points," says Kevin Tracey of the Feinstein Institute for Medical Research on Long Island, who is one of the pioneers of bioelectronic medicine.

Tracey, a former colleague of Ulloa's, adds that studies such as the one from the Rutgers group could help establish a physiological mechanism to explain why acupuncture might work as a treatment. Tracey's own research led to the founding of a company called SetPoint Medical in Valencia, Calif., which is developing an implantable device to activate a separate neuroimmune pathway to treat inflammatory diseases.

Testing Ancient Treatments

Acupuncture still has its critics at various ends of the medical spectrum. Some acupuncture proponents perceive a study on sepsis as a case of Western medicine finally conferring a belated blessing on techniques that have been accepted treatments for thousands of years. Skeptics of alternative medicine, meanwhile, criticize any investigation of acupuncture as a waste of limited research dollars on a folk remedy for which a firm scientific basis will never be found.

Steven Novella, president of the New England Skeptical Society, characterizes the sepsis study as having merely shown that a nerve responds to the application of an electric current. "Electroacupuncture itself is not a real entity, in my opinion," he says. "It is just electrical stimulation. Doing stimulation through an 'acupuncture needle' is meaningless—it's just a thin needle. There's nothing that makes it an acupuncture needle. And there is no evidence that acupuncture points exist at all."

For his part, Ulloa had no intention of trying to determine whether flows of vital energy, or *qi,* were making their way through the body's "meridians" based on the interpretation for how acupuncture works in Chinese traditional medicine. In fact, he agrees with Novella's argument about nerve stimulation. In the study, the researchers found no anti-inflammatory effect when a toothpick was used to probe ST36 Zusanli, in a manner similar to the way acupuncture needles had been inserted for centuries before the advent of electroacupuncture.

As a prospector for neuroimmune pathways, Ulloa insists his interest in exploring acupoints in his research has not flagged. "It is no coincidence that all acupoints but one—360 of 361 described in humans—are located in the proximity of a major nerve," Ulloa says. In his study, ST36 Zusanli led directly to the discovery of one of the most intricate neuroimmune circuits found to date. "Instead of testing millions of potential points, we reasoned that acupoints may provide an advantage in stimulating neuronal networks more efficiently," he says.

A few days after the acupuncture paper in *Nature Medicine* appeared, a study published in *Science Translational Medicine* documented that a component of the herb *Salvia miltiorrhiza,* another hand-me-down from the Chinese traditional medicine pharmacopeia, also turned out to have potent anti-inflammatory properties. The researchers from leading institutions who wrote that paper were taking the same path as Ulloa and his team, attempting to test whether an ancient treatment had through trial and error turned up some biological effect or therapeutic potential that could be subject to a rigorous testing regimen in the laboratory.

> KNOWLEDGE DERIVED FROM ALTERNATIVE MEDICINE MAY UNCOVER NEW NERVE PATHWAYS **THAT CAN REGULATE IMMUNE DISORDERS.**

In both reports, the authors were following the dictates that top-flight journal editors, article reviewers—and the skeptics themselves—endorse for evidence-based medicine. This type of study will certainly be more the exception than the rule. These same journals will never be publishing on feng shui and homeopathy—and the acupuncture entries in their pages will still be relatively scarce. But if scientists studying acupuncture or herbs can cross the high bars set by the scientific establishment, what's wrong with that? M

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MIND ARCHITECTURE

Keep It in Mind

What is consciousness? A neuroscientist's new book argues that it arises when information is broadcast throughout the brain

Quantum physicist Wolfgang Pauli expressed disdain for sloppy, nonsensical theories by denigrating them as "not even wrong," meaning they were just empty conjectures that could be quickly dismissed. Unfortunately, many remarkably popular theories of consciousness are of this ilk—the idea, for instance, that our experiences can somehow be explained by the quantum theory that Pauli himself helped to formulate in the early 20th century. An even more far-fetched idea holds that consciousness emerged only a few thousand years ago, when humans realized that the voices in their head came not from the gods but from their own internal spoken narratives.

Not every theory of consciousness, however, can be dismissed as just so much intellectual flapdoodle. During the past several decades, two distinct frameworks for explaining what consciousness is and how the brain produces it have emerged, each compelling in its own way. Each framework seeks to explain a vast storehouse of observations from both neurological patients and sophisticated laboratory experiments.

One of these—the Integrated Information Theory—devised by psychiatrist and neuroscientist Giulio Tononi, which I have described before in these pages [see "Ubiquitous Minds"; Scientific American Mind, January/February 2014], uses a mathematical expression to represent conscious experience and then derives predictions about which circuits in the brain are essential to produce these experiences. [Full disclosure: I have worked with Tononi on this theory.] In contrast, the Global Workspace Model of consciousness moves in the opposite direction. Its starting point is behavioral experiments that manipulate conscious experience of people in a very controlled setting. It then seeks to identify the areas of the brain that underlie these experiences.

Stanislas Dehaene, the French cognitive neuroscientist at the Collège de France in Paris who has devoted much of his career to studying the psychology of consciousness, has just published a compelling book on his investigations into how the Global Workspace Model maps onto the brain.

The model derives from the realization that whenever we become conscious of something—whether a familiar face in a crowd or the voice of a stranger—we can retain what we perceive in our mind for a brief period. This perception can remain in this short-term memory storage, a kind of mental scratch pad, even after the face has disappeared or the voice has died away. Cognitive scientist Bernard Baars of the Neurosciences Institute in La Jolla, Calif., who came up with the Global Workspace Model, took his central insight from the early days of artificial intelligence, in which specialized programs accessed a shared repository of information, the blackboard. According to Baars, it is the act of broadcasting data from the blackboard throughout a computational system, whether cybernetic or biological, that makes it conscious. Consciousness is just brain-wide sharing of information that is in the memory buffer of the blackboard.

This neural buffer does more than process recent sensory inputs. It can also call up a memory from long ago and move it into the buffer. Once information is loaded into this workspace, a host of powerful cognitive processes can make use of it. The data can be sent off to a particular brain area that processes language—a language module—where this knowledge can be readied for sharing with other people by formulating a spoken explanation: "Guess who I just saw over there." It can also be forwarded to a planning module to be reasoned about, and it can be stored in long-term memory. The act of transmitting these data from the brain's memory buffers to its various functional modules is what gives rise to consciousness.

Unfortunately, this workspace has extremely limited capacity. At any one time, we can be conscious of only one or a few items or events, although we can quickly shift things into and out of con-

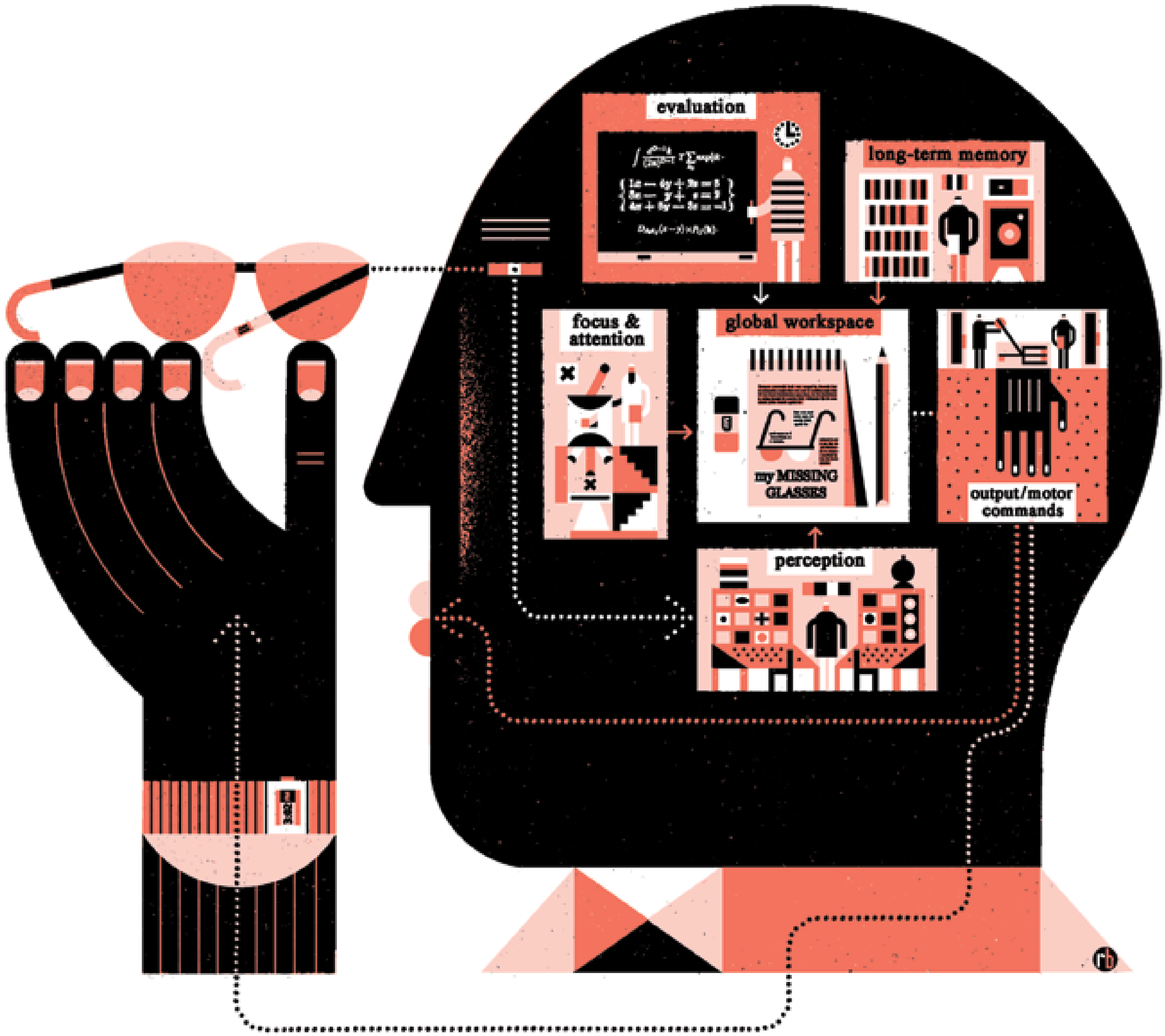
ONCE A MEMORY OR SENSORY INPUT IS LOADED INTO THE GLOBAL WORKSPACE, **COGNITIVE PROCESSES CAN MAKE USE OF IT.**

BY CHRISTOF KOCH

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

Send suggestions for column topics to editors@SciAmMind.com

SEAN McCABE



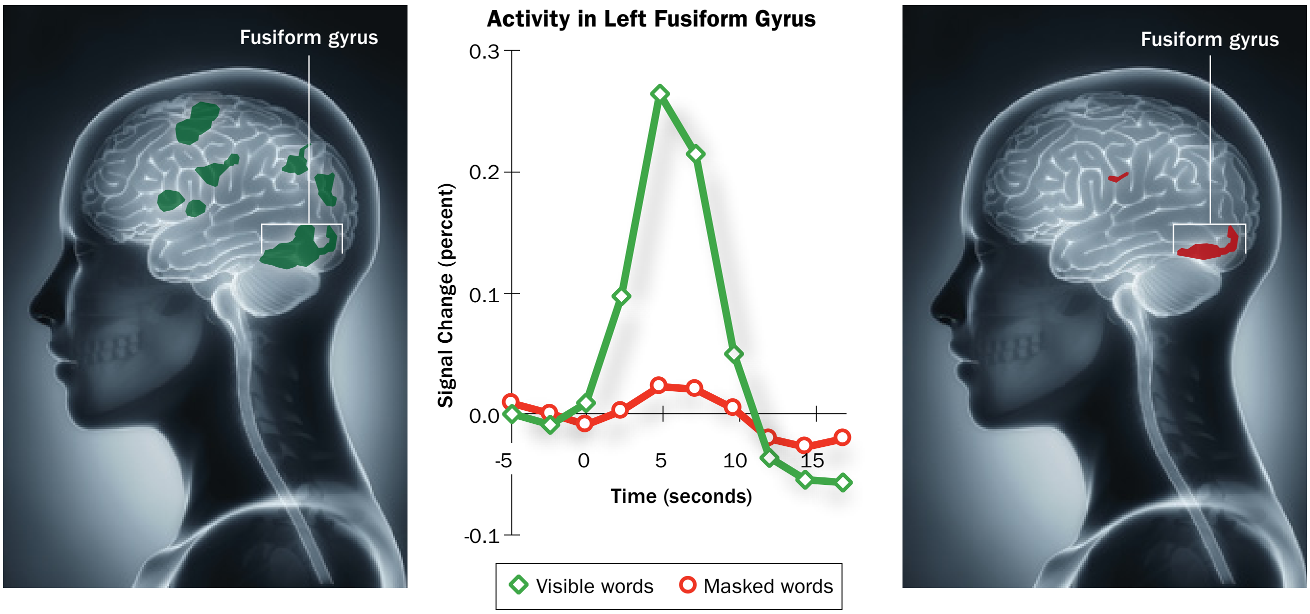
RAYMOND BIESINGER

Cognitive scientists Stanislas Dehaene and Bernard Baars have suggested that memories, sensory perceptions, judgments and other inputs are stored in a type of short-term memory called the global workspace. This buffer gives rise to consciousness when the collected information is broadcast throughout the brain to stimulate cognitive processes that then engage the motor system, spurring the body to action.

sciousness. New information competes with the old and may ultimately overwrite it. This limitation probably is an unavoidable design characteristic of any information-processing system that is overwhelmed by inflowing data streams and has to concentrate its most precious resources on dealing with a couple of critical items as fast as possible.

The brain compensates for the dearth of neural bandwidth by calling on a host of unconscious processes that either totally bypass this central scratch pad or interact with it below the level of awareness. The vast subliminal onslaught of data thereby turns sounds into meaningful words and photons into objects and identifiable people. These processes evaluate and weigh evidence, pass judgment and synchronize the movements initiated by the musculoskeletal system so that an organism can survive in a constantly and rapidly changing world. They are sophisticated and act quickly but do not share information with one another, nor do they transfer it into the common workspace. As with an intelligence agency, information is shared only on a need-to-know basis.

Yet these myriad agents of the uncon-



Presentation of a visible word to a viewer leads to a flurry of activity in many regions throughout the cerebral cortex—and in particular, the left fusiform gyrus, where words are processed (*left*). The activity is more than 10 times higher (*graph*) than if the displayed word is masked (*right*). The network of activated brain regions corresponds to the global workspace, a key set of neurons that are part of the brain's machinery for producing consciousness.

SOURCE: "CEREBRAL MECHANISMS OF WORD MASKING AND UNCONSCIOUS REPETITION PRIMING," BY STANISLAS DEHAENE ET AL., IN *NATURE NEUROSCIENCE*, VOL. 4, NO. 7; JULY 2001; THINKSTOCK (*heads*)

scious shape our daily routines. Because we have, by definition, no access to these subliminal events, we consistently underestimate their importance. Yet occasionally they manifest themselves quite dramatically. Japanese novelist Haruki Murakami put it well in a striking interview: "We have rooms in ourselves. Most of them we have not visited yet. Forgotten rooms. From time to time we can find the passage. We find strange things … old phonographs, pictures, books … they belong to us, but it is the first time we have found them."

Dehaene probes these unconscious lairs using a technique called masking. A picture, say, of a face or a word is briefly flashed onto a monitor, preceded and followed by images of a bunch of randomly drawn lines or a cloud of X's. These "masks" prevent the displayed face or word from becoming conscious—a subject reports seeing only a mask. Combining versions of this technique with recordings from electrodes implanted deep into the brain of patients monitored for epilepsy seizures, Dehaene and his colleagues demonstrated that the unconscious can process the meaning of word combinations—the brain responds differently to "happy war" than to "happy love"—implying that it has noticed the incongruence of having a word with a positive emotional meaning followed by a word with a negative one.

Dehaene and the distinguished molecular biologist Jean-Pierre Changeux have gone beyond this rather abstract model and are searching for the specific brain areas and populations of neurons that correspond to the global workspace. Their ongoing research using functional brain imaging and electroencephalographic electrodes placed on the skull has uncovered distinct neural signatures in these regions that appear to represent the theorized mental buffer.

THE ACTIVITY OF A PARTICULAR BRAIN NETWORK IS THOUGHT TO EVOKE **A TELLTALE SIGNATURE OF CONSCIOUSNESS.**

In one classic experiment, Dehaene and his colleagues had volunteers lie inside a magnetic resonance imaging scanner while they watched a stream of words on a computer screen, each one displayed for 29 milliseconds. Some of the words were masked, which triggered only a slight brain response. But when the words were legible, an avalanche of neural activity occurred.

The activated regions make up a dense tapestry of interlocking brain cells—specifically pyramidal neurons—that tie together the prefrontal cortex, the inferior parietal lobe, the middle and anterior temporal lobes and other brain regions. Axons, the wirelike extensions from a neuron's cell body, fan out from the brain's fissured surface, the cerebral cortex, to bind together vast reaches of neural topography. This network is where Dehaene and his colleagues have started to look both for the brain's scratch pad and for how signals streaming through this web of connections are communicated to the rest of the brain.

Whenever a stimulus is consciously perceived, its neuronal footprint—a particular type of brain activity—shows up in many parts of the cerebral cortex. Take, for instance, the intense electrical activity triggered by an image that passes into the primary visual cortex at the back of the head and from there to many cortical regions. As it reaches anterior regions of cortex, the signals increase in amplitude, prompting Dehaene to call it a neuronal avalanche.

The intense neuronal firing can be caught in the act with EEG electrodes by measuring the P300 wave, a brain wave that, in experiments, starts about 300 milliseconds after an image is projected onto a computer screen. As Dehaene's experiments demonstrate, becoming conscious of a sight or sound by having it broadcast throughout the brain from areas postulated to make up the global workspace often goes hand in hand with the presence of a P300 wave in the prefrontal cortex, a brain area associated with higher mental processes. Conversely, without the signature P300 wave, electrical activity dies out, and the image displayed is not consciously perceived. The information fails to enter the global workspace and so remains subliminal.

First Glimmers

Dehaene and his colleagues used this electrophysiological marker of conscious perception to map when consciousness first arises in five- to 15-month-old infants [see "The Conscious Infant"; Scientific American Mind, September/October 2013] and to devise a clever test for consciousness in severely brain-injured patients with whom no reliable communication using speech, eyes or gestures is possible. The tests depend on the ability of a conscious individual to detect a novel stimulus—imagine reading a book when your cell phone abruptly rings. This unexpected event can trigger a massive P300 wave that is readily noticeable. Yet when you do not pick up the phone and it rings again and again, you come to expect it, and the P300 becomes fainter until it cannot be detected.

In the laboratory, the researchers play a sequence of five simple tones: *beep beep beep beep boop*. The last odd-man-out tone generates a strong P300. When the entire sequence of five tones is repeated three times, the brain adapts to the deviant sound, and the consciousness marker disappears.

Then, along comes a *beep beep beep beep beep* sequence. As an attentive subject becomes conscious of the lack of a deviating sound in the fourth sequence, her brain responds with a P300 to the final *beep* because it was conditioned to expect a *boop*.

Preliminary trials using this test with brain-injured patients are intriguing. Patients in whom behavioral evidence indicates a minimal level of consciousness show this pattern of P300 activity on their EEGs, whereas those in a coma, thought to be without any sensation whatsoever, do not. Ongoing experiments seek to exploit the same odd-man-out paradigm in monkeys and in mice.

CONSCIOUSNESS AS A FORM OF BROADCAST TV **RAISES A SERIES OF UNANSWERED QUESTIONS.**

Proposing that what we consciously experience can be defined as the brain's ability to distribute information from the global workspace to the rest of the brain brings up several questions. Why and how, for instance, does broadcasting information from the global workspace give rise to consciousness? What message is being broadcast? Bloodborne hormones and chemicals that regulate neural activity also relay information throughout the body and brain. Yet we are not aware of them. Why not? And can data transmitted over the Internet or information coursing through the nervous system of a roundworm represent conscious activity? For now the Global Workspace Model avoids such thorny questions.

When the molecular-biologist-turned-neuroscientist Francis Crick and I started our joint work in the late 1980s on trying to understand the brain activity underlying vision and other mental processes, scant experimental work was dedicated to empirical studies of the hallmarks of consciousness.

As the work by Dehaene, Changeux and their colleagues makes abundantly clear, this sorry situation has changed radically. Their research program is beginning to untangle how the firing of networks of brain cells translates into this most mysterious of all phenomena. M

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SPECIAL REPORT HOW WE REMEMBER

THE ENGINE OF MEMORY

Even after his death, the famous amnesic H.M. is revolutionizing our understanding of how memory works and how we maintain it as we age

By Donald G. MacKay

ILLUSTRATION BY EIKO OJALA

At age 27, Henry Molaison, known to the public as H.M. until his death in 2008, underwent surgery that removed the brain's engines of memory formation. As a result, he could no longer remember new experiences in a normal way. As he aged, his established memories degraded abnormally as well, a mystery that an evolving body of work has begun to solve. *Clockwise from left:* H.M. appears as a high school senior, in his early 30s, at about age 50, at age 60, and as an old man.

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I remember meeting H.M. in the spring of 1967, when he was perhaps 40 years old and I was 16 years his junior. My mentor, Hans-Lucas Teuber, brought him to my tiny office across from the psychology department library at the Massachusetts Institute of Technology. I recall H.M.'s thin, smiling, rather handsome face as he squeezed into the doorway with Teuber, who introduced us as "Don" and "Henry," as if we might become buddies. I think I called Henry "sir" as we shook hands because he was already a minor M.I.T. celebrity. Teuber assured Henry that he would enjoy taking part in my experiment on sentence comprehension, something he was good at, and excused himself.

As we climbed the stairs to the testing room, it never crossed my mind that this quiet man would become a major focus of my research during the next half a century. I unlocked the door and seated Henry at a wooden desk facing mine, sunlight streaming into the room from large windows to my right. In front of me I had two stopwatches and a stack of 32 short sentences typed onto three-by-five index cards. I started a tape recorder and began what I thought would be a fairly routine experiment.

Since 1967 Henry's initials have become the most famous in the history of the brain sciences. (The public only learned his full name, Henry Molaison, after his death in 2008.) Henry's rise to fame began about 13 years earlier at age 27, when a neurosurgeon removed a small portion of his midbrain known as the hippocampal region. This removal largely cured Henry's life-threatening epilepsy but had an unintended side effect: for the remainder of his life, Henry could no longer learn new information in a normal manner, a condition that revolutionized the study of memory and the brain.

Studying Henry helped others before me to clarify the role of the hippocampal region in forming complex memories for novel, personally experienced events. My research with Henry showed that the hippocampal region also helps us to retain established memories, by essentially forming damaged memories anew. Without such renovation, we would forget forever.

This idea sweeps away the notion of memory degradation as a passive, inexo-

FAST FACTS

RESTORING REMEMBRANCES

1. People with amnesia have difficulty learning new information but (except for cases of Alzheimer's disease) never lose everything they have learned in the past.
2. Synaptic connections in the neocortex deteriorate with age, so that memories stored there become increasingly weak and fragmented. The memories that suffer the most are those we use infrequently.
3. The latest data on the famous amnesic H.M. suggest that one important role of the hippocampus is to craft new memories to replace those that have become degraded over the years.

If a knock at the door briefly called you away, when you returned, you needed to reintroduce yourself to Henry and again describe his task.

rable process. The mechanism by which we revive old memories appears to offset some of the recollection difficulties that occur during normal aging. Rather than allowing the pieces of our past to simply drift away with time, the brain stays actively involved in restoring damaged memories. These insights also solve a 100-year-old mystery in psychological research on amnesia. Until now, no one clearly understood why people with amnesia, who by definition have difficulty learning information encountered after their brain damage, usually have problems remembering information they learned many years before that damage.

"Who Are You?"

In the 1987 film *Overboard,* a socialite played by Goldie Hawn bumps her head falling from her yacht and suffers memory loss so complete that it destroys her identity. Movie plots invoking amnesia often feature dramatic scenes in which trauma immediately wipes out a character's past, but the protagonist can still form memories of new facts and experiences. Such cases are pure fiction. Real amnesic individuals have difficulty learning new information but (except for cases of Alzheimer's disease) never lose all of their past, whether caused by a brain lesion, a concussion, alcohol poisoning or a viral infection.

Henry became amnesic in 1953 after his operation, which removed the brain's central engines for memory formation. His ability to remember new experiences became severely impaired. Brief interruptions wiped out his extremely fragile memories for recent events (his episodic memories). If a knock at the door during your experiment called you away for even a minute, when you returned Henry might ask, "Who are you?" You needed then to reintroduce yourself and once again describe the task you wanted him to continue.

Henry could not make mental impressions of ephemeral experiences stick. In documenting such memory deficits, my mentor and others established the critical role of the hippocampal region in forming new long-term memories. Yet Henry's recollection of events and facts learned before his lesion seemed perfectly normal, at first. He pronounced everyday words fluently, easily asked questions such as, "Have we met before?" and lucidly answered questions about where he went to high school and where he was born.

In the 1960s psychologist Wayne Wickelgren, then at M.I.T., proposed that the hippocampal region facilitates the creation of permanent memories in the brain's exterior rind, the neocortex. These cortical memories take the form of strengthened connections among neurons. The neocortex thus resembles the repository, and the hippocampus acts

In this postmortem photograph of the brain of the amnesic H.M., white lines highlight the regions of the medial temporal lobes where a surgeon suctioned out part of his hippocampus, a brain region that governs long-term memory storage.

"POSTMORTEM EXAMINATION OF PATIENT H.M.'S BRAIN BASED ON HISTOLOGICAL SECTIONING AND DIGITAL 3D RECONSTRUCTION," BY JACOPO ANNESE ET AL., IN *NATURE COMMUNICATIONS*, VOL. 5; JANUARY 2014 like a builder of memories, whether these are episodic, such as my memory of meeting Henry, or factual (semantic), such as the meaning of a word. This idea, which emerged in large part from work with Henry, was a dramatic revision of earlier thinking. Previously researchers had conceived of the hippocampal region as a direct storehouse of memories. Because Henry's neocortex was unimpaired, it therefore made sense that his word memories, stored before his operation, would be intact.

So the day I met Henry, I assumed he would perform well on my sentence comprehension test. I instructed Henry to read 32 ambiguous sentences. For example, the sentence "I just don't feel like pleasing salesmen" could mean either "I don't want to please salesmen" or "I don't want agreeable salesmen around." Henry's task was to find and describe both meanings for each sentence as quickly as possible.

Henry discovered both meanings for just 20 percent of the sentences, whereas Harvard University students had no trouble identifying any of the ambiguities. Henry also took 10 times as long as the college students had—more than 49 seconds, on average—to begin his descriptions. And Henry's descriptions tended to be incomplete, inaccurate and difficult to understand. For example, at one point Henry explained the two meanings of "I just don't feel like pleasing salesmen" as follows: "The person doesn't like salesmen that are pleasing to him. Uh, and that personally he doesn't like them, and and [sic] personally he doesn't like them [sic], and then I think of a phrase that he would say himself, he doesn't, uh, pleasing, as conglamo [sic], of all of pleasing salesmen."

At the time, I did not know what to make of these observations. A confusing array of questions came to mind that I only later categorized and addressed. Why did Henry have difficulties understanding my sentences? Neurologists since 1874 had believed that a region of the cortex now known as Wernicke's area carries out sentence comprehension. Yet Henry's neocortex was undamaged. His incoherence also baffled me because Broca's area, in another part of the neocortex, was thought to be the engine that created grammatical sentences. And what did Henry mean by "conglamo"—a conglomeration? A concatenation? Or a fusion of both words?

At age 40, Henry seemed too young to be experiencing word-finding difficulties, but something was clearly happening to his lexical memories.

At age 40, Henry seemed too young to be experiencing word-finding difficulties, but something was clearly happening to his lexical memories. I just had no idea what that was. Only later would I discover a connection between Henry's damaged hippocampal region and his memory for words he had learned in adolescence.

A Type of Fastener Made of Nylon

After earning my Ph.D. from M.I.T. in 1967, I became a professor at the University of California, Los Angeles. For me, language proved to be a useful way to study many aspects of memory, including the impact of aging on our ability to remember familiar words. Unlike memories for personal experiences, which vary from person to person, we all learn the same spelling, meaning and pronunciation for words. The uniformity of word knowledge in young adults made it easy for me to determine whether aging was responsible for the deteriorating word memories of older adults.

My research during subsequent years delineated specific age-related changes in how we remember words. In 1990, for example, my colleagues and I reported that as we age, the ability to recall pronunciations of familiar but rarely used words declines systematically. When we gave people a definition such as "a type of interlocking fastener made of nylon," adults aged 65 and older could not bring to mind the word "Velcro" as often or as readily as adults 18 to 20 years old. For the older adults, the word more often remained on the tip of their tongue: they knew the meaning of the word, often its first speech sound (V) and its number of syllables but could not retrieve the entire word.

In 1998 my team published a related discovery: the ability to spell familiar but irregularly written words such as "rhythm," "physicist" and "yacht" also declines with aging. Adults 60 years or older in our experiments produced reliably more misspellings than young adults. Even though the older adults realized that they once spelled "bicycle" without difficulty, they could no longer remember whether it was spelled "bicycle," "bysicle" or "bisykle" until they reencountered "bicycle" in print.

Our discoveries indicated that normal adults older than 65 experience slight but reliable difficulties in retrieving lexical information learned decades earlier, difficulties that become progressively more severe with aging. At first, the information would come to mind after a delay, but as the memory grew more fragile over time, it often became irretrievable. At the extreme, even seeing the word failed to bring to mind its correct pronunciation, spelling and meaning.

THE AUTHOR

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(To learn what aspects of memory decline with age and what to do about it, see the box on the next page.)

Tip-of-the-tongue and tip-of-the-pen experiences are thought to arise when the relevant neural connections in the neocortex degrade. The representations of our knowledge of how to spell "rhythm" or pronounce "Velcro" weaken with time if these words are rarely spoken, seen or heard. Frequent use or recent exposure to a word strengthens those connections and prevents forgetting. Older people show no deficits in understanding, spelling or recalling words they often use, hear or write.

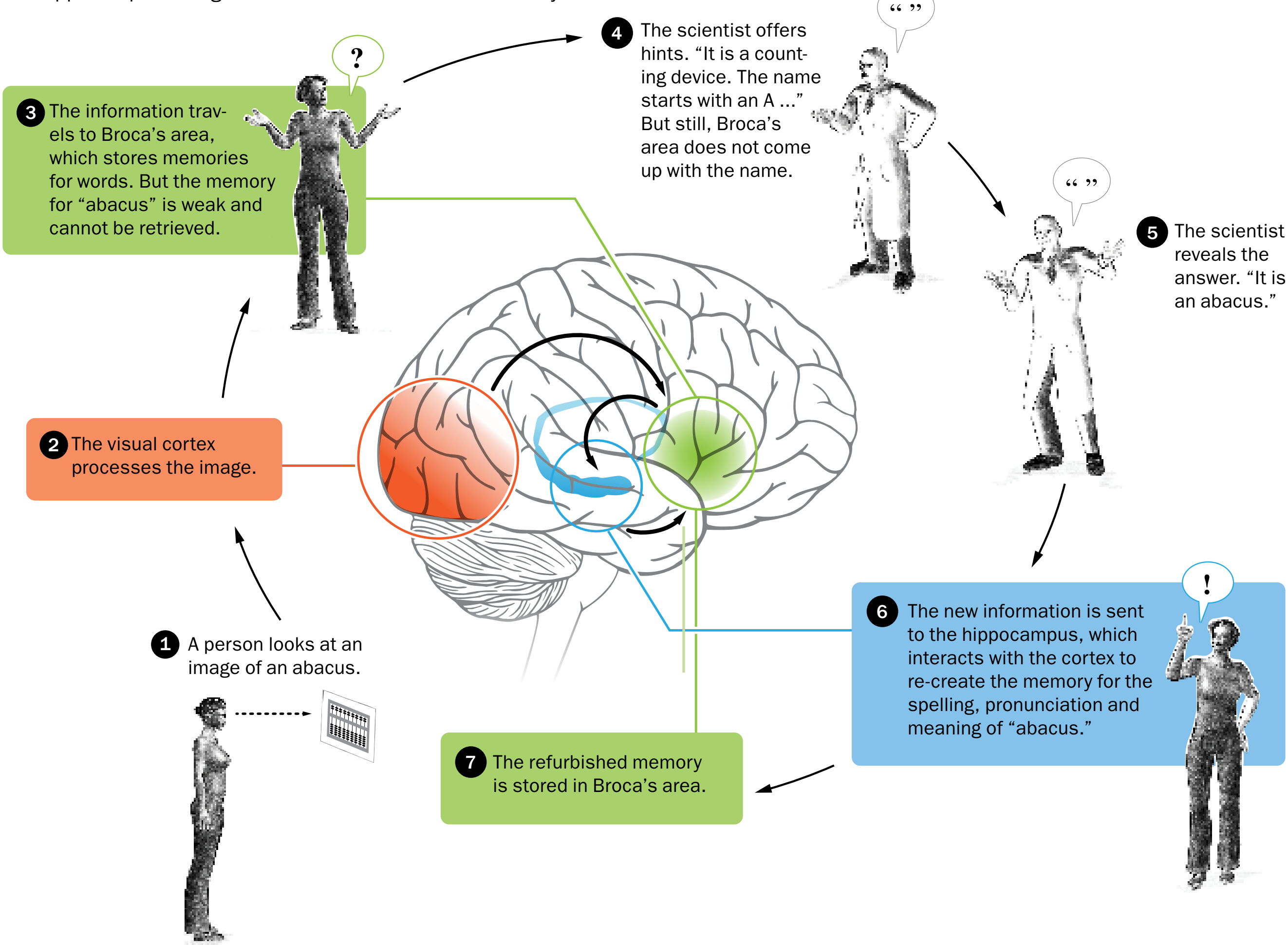
An Aging Amnesic

As I investigated the effects of normal aging on word memories, I returned to my 1967 questions about Henry's lexical memories. I reexamined a 178-page transcript of interviews with Henry recorded in 1970 by William Marslen-Wilson, a fellow graduate student at M.I.T. The recording revealed that at age 44, Henry experienced unusual difficulties retrieving rarely used words. Instead of describing people as "more relaxed," Henry said they were "more eased." Similarly, he referred to a model airplane as made of "bamboo" or "like wood" rather than "balsa." These errors haunted me, as I had never seen such lapses in someone so young. It was as if Henry's lexical memories were undergoing premature deterioration.

Then an idea came to me. Perhaps Henry's word-finding problems reflected an inability to relearn information he had completely forgotten. After all, his fundamental deficit was an inability to represent new information in his cortex. I reasoned that Henry's hippocampal damage may have prevented him from offsetting the degradation that accompanies normal aging. This inability could have transformed the usually minor word-retrieval problems of older adults into major impairments.

How to Restore a Memory

Our memories gradually degrade over time if we do not use them. The hippocampus, which governs memory formation, is now thought to engineer the restoration of fading memories in response to experience. For example, if someone has not recently encountered the name of an object such as an abacus, that individual may not be able to recall that name—which had been stored in Broca's area, a region that houses names and labels—when she sees a picture of an abacus. But when she is told the name, the hippocampus swings into action to re-create its memory in Broca's area.



TAMI TOLPA

But so far I only had hints that Henry suffered such severe memory gaps. To determine whether Henry's memories were in fact fading abnormally, I needed to compare his word knowledge in his early 70s with that of people with normal memory who resembled Henry in all other respects. I also needed to document how Henry's lexical memories changed during his lifetime. Evidence of unusual memory degradation might for the first time explain why most individuals suffering damage to the hippocampal region end up forgetting information learned before their lesion.

When Henry was 71 and 73 years old, I asked my postdoctoral fellow, Lori E. James, now a psychologist at the University of Colorado Colorado Springs, to fly to Boston to test Henry's lexical memory at M.I.T. I wanted to assess Henry's ability to define words, with questions such as "What does 'squander' mean?" and to see whether he could tell which words—"squander," say—are real and meaningful rather than invented. I also wished to evaluate how well Henry could retrieve the sounds of words for the purpose of naming familiar objects in pictures and reading rarely used words aloud. Finally, I was curious whether Henry could recall irregular spellings of words such as "rhythm."

James and I created sets of words that Henry had almost certainly used earlier in his life, based on the age at which each word is normally acquired and the extensive Marslen-Wilson transcript of words Henry had used in conversation at age 44. We categorized our words as high frequency or low frequency based on available statistics on how often people use them. (I discuss only our results for low-frequency words because Henry's performance for common words was unremarkable.)

Testing Henry was the easy part. I, along with my wife, Deborah M. Burke, a psychologist at Pomona College, and our colleagues then spent many years finding healthy individuals aged 71 or 73 years with normal memory whose education, intelligence, occupation and socioeconomic background were similar to Henry's. We culled our candidates from the records of more than 750 older adults in the participant pools of the U.C.L.A. Cognition and Aging Laboratory, the Claremont Project on Memory and Aging, and retirees from clerical or physical plant positions at the Claremont Colleges.

In the end, we found 26 individuals for suitable control groups. Comparing Henry's results with those of these individuals revealed dramatic deficits in Henry's lexical memories, as my colleagues and I reported in a series of papers that culminated in 2009. In our tests of word meaning, for instance, the 73-year-olds without brain damage correctly responded with "a type of bean or pea" to the question "What does 'lentil' mean?" Henry, on the other hand, told us: "That's a combination word, in a way, from 'lent' and 'till' ... (meaning) area and time of." Henry produced many such remarkable errors and generated fewer correct definitions than our comparison subjects, even for words that he used appropriately when he was younger. Henry also could not reliably distinguish low-frequency words from pseudowords such

Memory's Fountain of Youth

Like the rest of the body, the brain tends to decline with age. Yet science suggests ways to lessen the loss

L A HEUSINKVELD *Alamy*

First, a little perspective: not all aspects of memory decay. Older adults are just as able to understand sentences containing familiar words and to relearn forgotten information as when they were younger, though at a slightly slower rate. All behaviors are somewhat slower in older than younger individuals—a difference measured in thousandths of a second.

In some ways, cognitive function even improves with age. For example, vocabularies continue to expand up to age 80 and even beyond. As older individuals, we spontaneously use a greater variety of words and score higher on standardized vocabulary tests.

Older adults do encounter somewhat more trouble learning new uses for old words and remembering such things as a telephone number long enough to dial it. We also experience frustrating lapses in recalling the spelling of familiar, irregular words, such as "rhythm," and pronunciations—especially for the names of places and people—that we learned decades earlier.

Recent research, including my own, suggests that older adults can counteract these changes. The key is exposure. Engaging in social situations helps to protect numerous language-related, among other, facets of memory. Before meeting up with friends, we can rehearse their names so as to avoid the embarrassment of forgetting them. We can preserve our spelling and word-retrieval skills by playing games such as Scrabble in which we exercise those skills rather than engaging in passive activities such as watching television.

We can prevent the deterioration of areas of expertise—say, public speaking, chess or playing the piano—by continuing to practice or play. More generally, we can engage in lifelong learning of various forms. After all, learning and relearning—reinstating old memories—are ways the hippocampal region keeps all of us young. *—D.G.M.*

as "frendlihood" and "quintity." In contrast, the other 73-year-olds made accurate distinctions 82 percent of the time, and Henry himself scored at the 86 percent level on this same test at age 57.

When we instructed participants to read aloud words typed on index cards, Henry misread "triage" as "triangle," "thimble" as "tim- … tim-BO-lee" and "pedestrian" as "ped-AYE-ee-string." Henry's reading errors were far more numerous than the older adults we later tested. Apparently Henry could not remember how to pronounce multisyllabic words in which variables such as syllable stress patterns and certain letter sounds (such as whether to pronounce the e's in "pedestrian" as long or short) are unspecified.

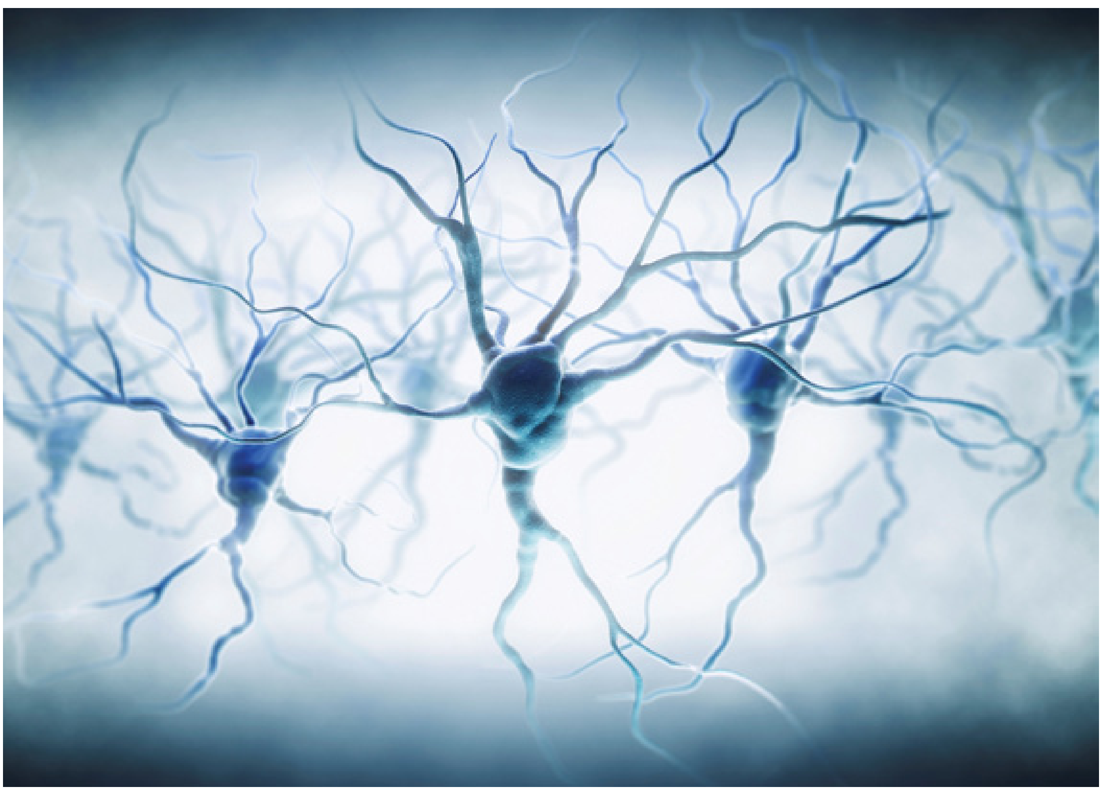
What's in a Name?

Henry's problems were similarly apparent in the so-called Boston naming test. In this test, people are supposed to identify common objects depicted in line drawings. If a subject cannot recall the name of the object, the experimenter provides phonological cues—for example, "it begins with 'tr'"—followed by a verification question containing the word itself: "Do you know the word 'trellis'?" Although he had been familiar with the target names at a younger age, Henry correctly named fewer pictures than others his same age, benefited less than they did from the phonological cues, and produced more erroneous answers involving incorrect speech sounds. For instance, Henry called a snail a "sidion," indicating severe degradation of his phonological memory for this familiar word.

To the question, "What does 'lentil' mean?" Henry told us: "That's a combination word, in a way, from 'lent' and 'till' … (meaning) area and time of."

In our spelling task, participants heard an irregularly spelled word such as "bicycle" and saw it spelled with a missing letter, as "bic_cle." They were asked to choose one of two letters ("i" or "y") to correctly fill in the blank. Henry chose the correct letter for 65 percent of the words, whereas our comparison subjects did so 82 percent of the time, suggesting extensive erosion of Henry's memories for irregularly spelled aspects of familiar words.

We next documented the trajectory of Henry's decline between his 40s and 70s. By comparing our results with those of others, we learned that Henry's lexical memories deteriorated dramatically



Our memories are stored in the cerebral cortex as changes in the connections between neurons (*left*). As we age, the neural ties representing our memories weaken, and we forget.

over the years, beginning in his late 50s. For instance, in a 1983 study by psychologists John Gabrieli, Neal Cohen and Suzanne Corkin, all then at M.I.T., Henry at age 57 showed a small but reliable deficit in distinguishing low-frequency words from pseudowords. At age 73, he showed significantly greater difficulties in the same task. Similarly, Henry had no problems naming pictures at age 54, according to a 1984 study by Corkin. Yet at age 73, Henry produced dramatic word substitutions such as "compass" for "protractor," circumlocutions such as "ice clippers" for "tongs," and neologisms such as "trake" for "trellis."

In word-reading tests, Henry exhibited small deficits at age 67 in a 1993 study by Corkin and her graduate student Bradley R. Postle. In our studies, his losses were more glaring for the identical words. At age 71 he misread 67 percent of the words versus a mean of 9 percent for our control subjects. Just two years later his deficit for the same words was even greater and included new types of errors such as segment-omission errors—for instance, the reading of "affirmation" as "formation."

Just as a builder can make a new structure or repair a damaged one, so could the hippocampus craft new memories to replace degraded recollections.

Memory Maintenance

Psychologists have known for decades that synaptic connections in the neocortex deteriorate with age, so that memories we have stored there become increasingly weak and fragmented. The memories that suffer most are those we recall infrequently. If we have not thought about, heard or seen something recently, that information is vulnerable—and more so the older we become.

In his 50s, 60s and 70s, Henry's difficulties remembering word knowledge he rarely used or encountered became progressively worse, and the decline for him was much steeper than for typical adults of the same age and background. We reasoned, therefore, that the hippocampal complex must be involved in preserving old memories as well as making new ones. Just as a builder can make a new structure or repair a damaged one, so could the hippocampus craft new memories to replace those that have been degraded or fragmented with time.

Such rebuilding might occur whenever someone reencounters a forgotten word or a personal anecdote from the past. In this way, recent exposure and learning could shore up a shattered memory and reduce the rate of loss. In Henry's case, this hippocampal maintenance system was defunct. Henry had no way of rejuvenating depleted memories through experience and relearning—leading to his accelerated decline.

To support this theory, we would like to determine whether other people with amnesia and hippocampal region damage eventually experience exaggerated or faster than normal degradation of memories for rarely used information. We also want to find out whether healthy older adults re-create memories that have decayed from aging and lack of use as they naturally reencounter the missing information.

From personal experience as an older adult, I believe that we can and often do refurbish fragmented recollections. When I reread my story about meeting Henry, I checked the date of our meeting by looking at my unpublished report, written soon after the experiment. Although I had been absolutely certain that I had met Henry in 1967, the report indicated 1966 as the time of the test, showing we had met one year earlier than I had remembered, a fact that I will not soon forget!

Some episodic memories are impossible to check and correct, however. As I reread my description of Henry and me climbing the stairs to our testing room, I suddenly recalled that Henry had taken out something resembling an oversize business card and proceeded to tell me a story about rifles. I can no longer retrieve the specifics of Henry's rifle story, and I have no way of revisiting this 1966 incident to renew my memory for it. As a result, the details of the rifle story will slide even further into oblivion, much like Henry's own memories did for aspects of the meaning, spelling and pronunciation of rarely used words. **M**

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- **Trying to Forget.** Ingrid Wickelgren; January/February 2012.

The Anatomy of AMNESIA

New findings on people with a damaged hippocampus suggest a bold rethinking of the way we map the brain By Felipe De Brigard

ILLUSTRATION BY EIKO OJALA

An attractive way to think of the brain is as an atlas of the mind.

In 19th-century views of neuroanatomy, mental faculties were housed in specific regions of the brain. Though roundly debunked, recent thinking in neuroscience has similarly tended to identify brain areas with psychological concepts, such as memory and emotion.

JONATHAN KITCHEN *Getty Images*

Continents of brain cells are given monikers such as "emotion" and "perception." Within them, independent countries go by names such as "vision" and "audition."

The labels are not without reason. Landmark cases of people with unique forms of brain damage have allowed neuroscientists to isolate specific regions that appear vital to a particular skill or psychological process. And no case is more famous in neuroscience than that of Henry Molaison, better known as H.M.

H.M. suffered from severe epilepsy. In 1953 neurosurgeons tried out a new technique to ease his seizures, which involved surgically removing his hippocampus, a small, C-shaped structure in the middle of the brain, and some adjacent areas. Little did they know that the procedure would knock out H.M.'s ability to form new memories.

He could still remember experiences of his childhood, though. In numerous tests, he demonstrated that other cognitive functions, such as working memory, language, perception and reasoning, remained intact as well. With great practice, he could acquire new skills, although he never became aware of his own learning. As a result, psychologists and neuroscientists concluded that the hippocampus is dedicated to acquiring long-term conscious memories but is unnecessary for pretty much anything else.

This claim became part of the core doctrine of neuroscience. It has featured, unquestioned, in almost every brain science textbook of the past 50 years. A growing body of evidence, however, is challenging the idea that the hip-

FAST FACTS

THE SEAT OF MEMORY?

1. A brain region called the hippocampus has primarily been viewed as a mechanism for acquiring long-term conscious memories.
2. Recent findings, however, suggest that the hippocampus also plays a role in imagination, language, vision and numerous other mental functions.
3. These results indicate that areas in the brain most likely do not map neatly to psychological terms such as memory and perception.

pocampus is the seat of memory. It now seems that this brain area is key to a dazzling array of skills tied to basic human experience. Which brings us to an inevitable question: What does the hippocampus do?

The Brain's Sea Horse

When Venetian neuroanatomist Julius Caesar Aranzi first described these seven centimeters of brain tissue in 1587, he likened the structure to a sea horse (or *hippo*, "horse," and *kampus*, "sea monster"). It is nestled in the middle of the brain within the limbic system, a set of areas that serve to regulate emotions, among other basic processes. Before H.M.'s surgery, the function of the human hippocampus was largely unknown. Indeed, until the 1930s the prevailing belief was that the hippocampal region supported our sense of smell or, perhaps, our capacity to navigate.

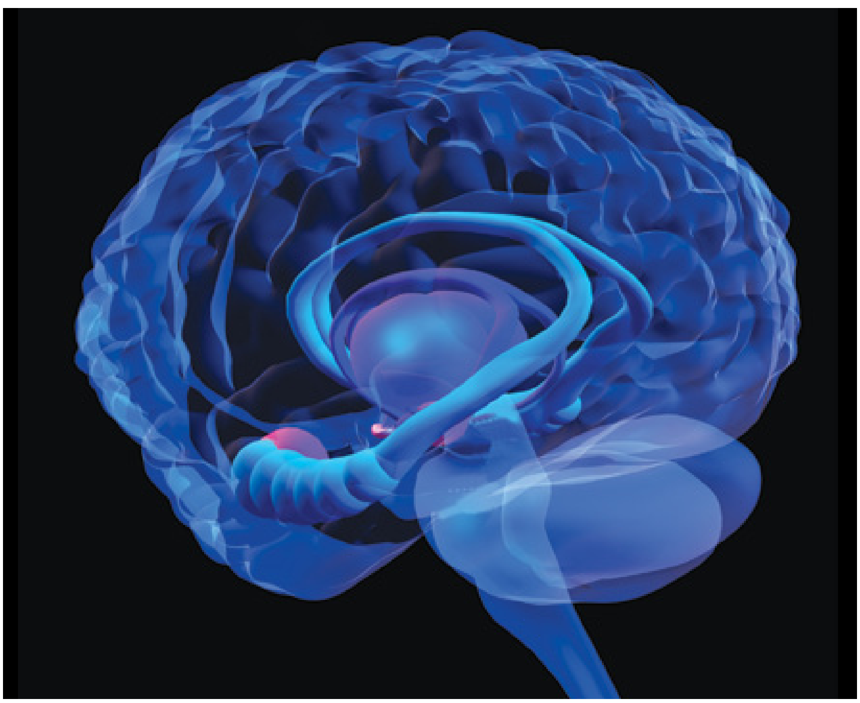
Observations of H.M.'s amnesia gave rise to the idea that the hippocampus and its neighboring areas—termed the hippocampal complex—were necessary for encoding new memories of a certain type, those that require conscious and voluntary processing. These recollections, such as thinking back on one's first day in school or knowing that the capital of France is Paris, are called declarative memories. Nondeclarative (or implicit) memory was spared for H.M.: in one test, he demonstrated that with sufficient practice he could learn to draw a complicated and unfamiliar star-shaped pattern. He even managed to retain this proficiency for up to a year, despite the fact that he never remembered—declaratively, that is—having performed the task before.

H.M. also scored on par with healthy control subjects on a wide number of visual and linguistic tasks. In a comprehensive report published 14 years after his surgery, H.M's neuropsychologist, Brenda Milner, and her colleagues wrote that his linguistic comprehension remained "undisturbed: he can repeat and transform sentences with complex syntax, and he gets the point of jokes, including those turning on semantic ambiguity." We were also told that his capacity to retain information for a short time—his working memory—was preserved, as was his intellectual capacity. It seemed quite clear that the hippocampus's job was to encode declarative information.

A growing body of evidence is challenging the idea that the hippocampus is the seat of memory. It now seems that this brain area is key to a dazzling array of skills tied to basic human experience.

If only it were so simple. As H.M. aged (he lived until he was 82), his language faculties decayed more rapidly than did those of other people his age, revealing that the hippocampus helps us communicate. [For more on H.M.'s language abilities, see "The Engine of Memory," by Donald G. MacKay, on page 30.] Or consider the claim that the hippocampus is not involved in learning a new skill through repetition. Although he could technically pick up new skills, it took H.M. three or four times as long to reach the same level of mastery as healthy people.

Moreover, H.M. might have been less flexible than people normally are in their skill learning. In a 2010 study neuropsychologists Shumita Roy and Norman Park of York University in Toronto introduced seven people to several unfamiliar tools. One participant had a damaged hippocampus, and the other six served as controls. As expected, with practice all



AP PHOTO

The hippocampus, highlighted here with a rattlelike section toward the front of the brain, is a key structure in the formation of memories. Yet it also does much more.

THE AUTHOR

FELIPE DE BRIGARD is assistant professor in the department of philosophy, the Center for Cognitive Neuroscience, and the Duke Institute for Brain Sciences at Duke University.

People with damage to their hippocampus often have trouble identifying odd features in scenes. And when they are asked to imagine themselves in a certain scenario, such as relaxing on a sunny beach, their descriptions are far less vivid than those of healthy people.

"As for seeing, I can't really, apart from the sky. I can hear the sound of seagulls and of the sea … um … I can feel the grains of sand between my fingers …"

JOHN WILHELM *Getty Images* (top); ALFONSE PAGANO *Getty Images* (bottom)

seven people got better at using these novel tools. Yet when tested a few days later, only the healthy subjects could still operate the tools. The affected patient could not even recall how to grasp them, let alone how to handle them. In short, adopting a new skill is not simply rehearsing something until it becomes automatic. We need to be able to bring other information back to mind as well.

The timing of a task can also wreak havoc on learning if a hippocampus is not around to help. A 2013 study by psychologist Karin Foerde of Columbia University and her colleagues revealed that individuals with hippocampal damage are unable to learn from feedback if it is delayed by even six seconds, as opposed to provided immediately. This was yet another ability that H.M. was believed to have retained, perhaps erroneously.

A Jack of All Trades?

The hippocampus even appears to help us see. Cognitive neuroscientist Morgan Barense of the University of Toronto, for example, compared the visual acuity of people with and without damage to the hippocampus. She observed that when a visual scene is complex, with objects overlapping and occluding one another, the patients' performance fell well below that of healthy subjects. A study from 2009 also supports the notion of a perceptual role for the hippocampus. Psychologists Donald G. MacKay of the University of California, Los Angeles, and Lori E. James of the University of Colorado Colorado Springs showed H.M. and several control subjects pictures of odd scenes, such as a bird flying inside a fishbowl or a door with its hinges on the same side as its knob. The task was to identify all the elements of the image that were wrong.

H.M. fared significantly worse than his healthy counterparts in two ways. He identified fewer wrong elements and misidentified as wrong more correct elements. In both studies, he seemed to struggle when trying to make sense of familiar pieces of information assembled in a manner or context that was novel.

What about reasoning and higher-order cognition, which appeared to be preserved in H.M.? One exception is imagination. In a striking demonstration published in 2007, Demis Hassabis, then at University College London, and his colleagues asked five individuals with hippocampal damage and 10 control participants to picture themselves in a certain place. In a representative response to the cue, "Imagine you are lying on a white sandy beach in a beautiful tropical bay," one patient replied:

"As for seeing, I can't really, apart from the sky. I can hear the sound of seagulls and of the sea ... um ... I can feel the grains of sand between my fingers ... um ... I can hear one of the ship's hooters [laughter] ... um ... that's about it."

When a researcher asked the patient, "Are you seeing this in your mind's eye?" the person said, "No, the only thing I see is blue."

In stark contrast, a healthy subject began a lengthy response in this way:

"It's very hot, and the sun is beating down on me. The sand underneath me is almost unbearably hot. I can hear the sounds of small wavelets lapping on the beach. The sea is a gorgeous aquamarine color. Behind me is a row of palm trees, and I can hear rustling every so often in the slight breeze."

Yet not all aspects of imagination are equally affected, as researcher Elizabeth Race of Boston University and her collaborators found in 2011. They compared how individuals with hippocampal damage and healthy participants fared when thinking about hypothetical events in their own life versus imagining a story based on a picture of others, such as a family at a picnic. Those who had damage struggled to imagine events in which they themselves might have participated, but they had no trouble weaving a narrative around the picnicking strangers.

Perhaps most surprising is the considerable body of research that now suggests that even working memory involves the hippocampus. Multiple neuropsychological tests had suggested that H.M.'s working memory was intact because he was able to follow simple sequential instructions and perform basic mental arithmetic without trouble. But keeping in mind unfamiliar objects for a few seconds or briefly retaining a complex scene seems to pose a challenge to people with hippocampal damage. Perhaps because the initial studies on H.M. used well-known items and familiar information, his probable deficits in these areas never surfaced.

A New Way of Thinking

So the lesson we thought we had learned from H.M., namely that the hippocampus's role is to encode declarative information into long-term memory, has been muddled by recent evidence. So what does the hippocampus in fact do?

One hypothesis is that it helps us bind together new information and integrate it with that which we have already learned. It might also allow us to connect information about individual items recorded in memory with new contexts. There may be others. Given the variety of cognitive activities for which the hippocampus appears to be essential, discovering the right conceptual framework remains a fascinating question—one that H.M. helped to formulate.

Perhaps, then, the real lesson of H.M. is the opposite of what was long taught: that we should be very careful when identifying mental terms—such as memory—with specific neural structures, such as the hippocampus. Neuroscientists widely accept that virtually every mental process invokes multiple brain regions. Yet we all, scientists and laypeople alike, rely on familiar notions such as memory and perception to frame our investigations of the mind and brain.

At a time in which so many scientific projects—the BRAIN Initiative in the U.S. and the Human Brain Project in Europe, among others—aim to produce "maps of the brain," we best not forget this lesson from H.M. The organizational principles of the brain might not mirror the categories we use to describe the mind's many functions. The brain is not an atlas of the mind. M

Perhaps the real lesson of H.M. is the opposite of what was long taught: that we should be careful when identifying mental terms—such as memory—with neural structures, such as the hippocampus.

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The influence of fathers on their teenage children has long been overlooked. Now researchers are finding surprising ways in which **dads make a difference**

Where's DAD?

By Paul Raeburn | *Photoillustrations by* C.J. Burton

Adapted from *Do Fathers Matter? What Science Is Telling Us about the Parent We've Overlooked,* by Paul Raeburn, by arrangement with Scientific American/Farrar, Straus and Giroux, LLC.

In 2011 administrators at Frayser High School in Memphis, Tenn., came to a disturbing realization. About one in five of its female students was either pregnant or had recently given birth. City officials disputed the exact figures, but they admitted that Frayser had a problem. The president of a local nonprofit aimed at helping girls blamed the disturbing rate of teen pregnancy on television.

She pointed to the MTV shows *16 and Pregnant* and *Teen Mom*. "So much of our society is sexually oriented," she said, arguing that the fixation on sex was enticing girls to have unprotected sex earlier and more often. A lot of us might say the same thing. We know that teenagers are impressionable, and the idea that they would be swayed by MTV makes sense.

But psychologists Sarah E. Hill and Danielle J. DelPriore, both at Texas Christian University, took note of a more subtle fact about Tennessee. Nearly one in four households was headed by a single mother. For Hill and DelPriore, that observation was a tip-off that something entirely different was going on. "Researchers have revealed a robust association between father absence—both physical and psychological—and accelerated reproductive development and sexual risk-taking in daughters," they wrote in a 2013 paper. You might expect sexual maturation to be deeply inscribed in a teenager's genes and thus not likely to be affected by something as arbitrary and unpredictable as whether or not girls live in the same house as their father. Yet the association is quite clear. The problem comes in trying to explain it. How could a change in a girl's environment—the departure of her father—influence something as central to biology as her reproductive development?

I put that question to Hill. "When Dad is absent," she explained, "it basically provides young girls with a cue about what the future holds in terms of the mating system they are born into." When a girl's family is disrupted, and her father leaves or is not close to her, she sees her future: men don't stay for long, and her partner might not stick around either. So finding a man requires quick action. The sooner she is ready to have children, the better. She cannot consciously decide to enter puberty earlier, but her biology takes over, subconsciously. "This would help facilitate what we call, in evolutionary sciences, a faster reproductive strategy," Hill said.

In contrast, a girl who grows up in a family in which the bond between her parents is more secure and who has a father who lives in the home might well (subconsciously) adopt a slower reproductive strategy. She might conclude that she can take a bit more time to start having children. She can be more thorough in her preparation. "If you're going to have two invested parents, you're investing more reproductive resources. If the expectation is you are not going to receive these investments, you should shift toward the faster strategy," Hill explained.

FAST FACTS
OF FATHERS AND TEENS

1. Fathers have long been neglected in research on child and family psychology, but recent work is identifying numerous ways in which they affect the development of their teenage children.
2. Among them are unexpected effects on the reproductive development of daughters and the cultivation of empathy in children of both sexes.
3. The new research suggests that a father's love and acceptance are at least as important as the love and acceptance of a mother.

The Missing Link

For a long time, until women began entering the workforce in bigger numbers in the 1960s and 1970s, fathers had a uniquely valuable familial role to play. They brought home the paychecks that housed and fed their families and provided a

The discovery of the father is one of the most important developments in the study of children and families. **Our failure to address the question of fathers' value is more than simply a matter of academic bickering.**

little extra for dance lessons, Little League uniforms and bicycles for the kids. Although bringing home a paycheck might not seem like the most nurturing thing a parent could do, it was vital: nothing is more devastating to the lives of children than poverty. Keeping children fed, housed and out of poverty was significant.

But was that it? What else could fathers claim to contribute to their children? The record shows that fathers have been widely overlooked in scientific studies. For example, in 2005 psychologist Vicky Phares of the University of South Florida reviewed 514 studies of clinical child and adolescent psychology from the leading psychological journals. Nearly half of them excluded fathers.

The situation has now begun to change. The discovery of the father is one of the most important developments in the study of children and families. Our failure to address the question of fathers' value is more than simply a matter of academic bickering. It is reflected in the shape of the American family. Fathers are disappearing: fewer dads are participating in the lives of their children now than at any time since the U.S. began keeping records. This shift matters because the effects of a missing father can be profound and counterintuitive—as in the age at which a daughter enters puberty.

Daughters at Risk

Yet the links between puberty and a father's presence are just associations. They do not reveal what causes these changes. In the ideal experiment that would answer this question, we would assemble a group of families and randomly assign some of the fathers to abandon their families and others to stay. Obviously, this proposal is not likely to win approval from an ethics board. So what is the next best thing? Hill and DelPriore designed an experiment in which young women—some of them teenagers and others just past their teen years—were asked to write about an incident in which their father supported them and then were encouraged to write about a time he was not there for them. Then they were asked about their attitudes toward sexual behavior. If the researchers' hypothesis was correct, memories of unpleasant father experiences would

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lead the young women to express more favorable views of risky sexual behavior. Pleasant memories of their fathers should push them in the opposite direction.

And that is what happened. Women became "more sexually unrestricted" after recalling an incident in which their father was disengaged, Hill explained. Further experiments showed that father disengagement did not change women's views of other kinds of risky behavior; for instance, they were not more likely to ride a bike without a helmet. The effect was limited to sex.

Hill told me that her research rests heavily on work by Bruce J. Ellis of the University of Arizona, who helped to establish the connection between father absence and adverse outcomes for daughters. Ellis calls himself an evolutionary developmental psychologist. He wants to know whether Charles Darwin's theory of natural selection can help explain how children's environments shape their development—precisely the question that came up in Hill's study. His research on fathers began in 1991, with efforts to test an interesting theory. The idea was that early childhood experiences could change the way children later seek their mates. Early experience seems to "set" the reproductive strategy that girls use later in their lives. This is not true of boys, possibly because they have a different reproductive strategy.

In a series of studies beginning in 1999, he found that when girls had a warm relationship with their fathers and spent a lot of time with them in the first five to seven years of their lives, they had a reduced risk of early puberty, early initiation of sex and teen pregnancy. As Ellis continued this work, however, he became increasingly frustrated. Clearly,

BUILD YOUR OWN FAMILY Not all families have two deeply committed parents. For everyone else, here are the essentials for raising kids right

By Roni Jacobson

Single-parent households are a fact of life. One in four children in the U.S. lives with only one parent, usually a single mom, according to census data. Yet a child without two committed parents need not face a disadvantage because of that fact.

Distilling a large body of research down to its essentials reveals a few key factors. The most important elements of child rearing are not the identity or gender of the adults involved but the quality of care coming from those people, as well as its consistency over the years. In cases where one parent is absent, unreliable or uncommitted, research suggests that families keep the following priorities in mind.

COMMIT

Raising a child has always been tough, but rarely does one parent manage it alone. In a study on fragile families by a group of researchers at Columbia University and Princeton University, only 17 percent of single moms reported that they were raising their children completely on their own—most of them had help from the child's father, their own parents, other relatives or friends.

Yet consistency is key. "It's not enough that there just be an adult that's on duty—one year it's the mom, the next year it's the grandma, the next year it's the biological father. You need somebody who is going to be there for the long haul," says Anne Martin, a developmental psychologist at Columbia University. "The child needs to feel safe and secure in his or her environment to grow intellectually and emotionally."

For older children, mentors such as teachers, coaches or religious leaders can provide support, as long as those commitments are enduring. The mentoring organization Big Brothers Big Sisters, for example, requires volunteers to commit for at least a year, with the average mentor-mentee relationship lasting two years and three months.

COLLABORATE

The harsh reality, though, is that the primary parent in a fractured family often struggles to find someone who can shoulder a decade or more of unflagging support. Take that study from Columbia and Princeton: most of the unmarried fathers initially said they wanted to be involved in their child's life. Yet three years after their baby's birth, almost half of the fathers living apart had not been in recent contact with their child.

One way to help engage these dads and other caregivers is to focus on their relationship with the mother. Clinical psychologist Kyle Pruett of the Yale University Child Study Center highlights this variable in his efforts

ISTOCKPHOTO

the association between fathers and daughters was profound. Yet he could not determine whether the parental behavior *caused* the consequences he was seeing in the daughters. An alternative was that girls who begin puberty early and engage in risky sexual behavior do so because they inherited certain genes from their parents. Fathers might pass on genes linked to infidelity to their daughters, in whom they could be associated with risky sexual behavior and early puberty. Or something else in the family's environment could be responsible for the changes in their daughters.

Ellis came up with an innovative way to pose the question. He considered families in which divorced parents had two daughters separated by at least five years in age. When the parents divorced, the older sister would have had five more years with a father's consistent presence than the younger sister. If

> "The great emphasis on mothers and mothering in America has led to an **inappropriate tendency to blame mothers for children's behavior problems and maladjustment** when, in fact, fathers are often more implicated than mothers in the development of problems such as these," Rohner says.

to bring unengaged fathers into their children's life. "Focusing on the men alone turned out to be a waste of money and research efforts," Pruett says. "We have found that the best way to support the mother is not to deal with the father separately but to deal with him in context with her."

According to Pruett, many moms must first learn to accept that their helper will have a different parenting style than they do and not try to mold the other caregiver's behaviors to mimic her own. Duplicating efforts can even backfire, as researchers at Ohio State University found in a study published in 2011. One year after resident fathers took over parenting tasks from a mother, the couples in the study had become more combative and more inclined to undermine each other. A better strategy, the authors suggest, is for the two to decide together on their different spheres of influence, perhaps with one parent in charge of bathing and the other in control of preparing meals.

A positive relationship between caregivers can have a major impact on a child's psychological development. In a 2013 study of African-American families, researchers at the University of Vermont and the University of North Carolina at Chapel Hill found that the better the relationship between a single mother and her primary helper, the fewer mental health and behavioral problems in the children. A better bond can also reinforce nonresident fathers' commitment to their kids. In a 2008 study led by sociologists Marcia Carlson and Lawrence Berger of the University of Wisconsin–Madison, fathers who lived apart but exhibited good communication and teamwork with a child's mom were more likely to still be involved in their children's life five years after they were born, regardless of whether the parents were romantically involved.

ENGAGE

Women today continue to perform the majority of primary caregiving tasks, such as feeding, bathing and comforting children. Fathers, on the other hand, tend to take part in supplementary activities, such as play, which matter less to a child's survival but assist their cognitive development. As a result, the quality of their involvement appears to matter more for children than the quantity.

In a 2013 study of fathers living apart from their biological children, for instance, scientists at the University of Connecticut and Tufts University found that neither monetary contributions nor the frequency of visits had a significant effect on the child's well-being. Rather the critical factor was how often the father engaged in child-centered activities, such as helping with homework, playing together, or attending sports events and school plays.

This kind of involvement promotes cognitive development by "stretching the child's current level of ability, building on what they know right now and expanding it," Martin says. Known as scaffolding, such engagement helps children develop logical reasoning and problem-solving skills that translate into various situations in life. In households with two married, biological parents, both mothers and fathers tend to scaffold equally. Children living apart from their fathers, however, are less likely to receive the same exposure to cognitively stimulating activities, according to a 2013 study by Carlson and Berger.

Helper parents are therefore especially important for promoting children's intellectual growth. A recent review in the *Journal of Community Psychology* found that mentors—including relatives, teachers or other involved adults—advance children's academic achievement by introducing them to new ideas and experiences and finding "teachable moments" that challenge them to think critically.

Knowledge building can happen anywhere, not only on outings to museums or in the classroom but also at dinner, while playing, or when driving to and from soccer practice. The key, researchers say, is paying attention to what children are interested in and following their lead.

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earlier than their older sisters—but only in homes in which the men behaved badly as fathers. "We were surprised to get as big an effect as we did," Ellis told me. The conclusion was that growing up with emotionally or physically distant fathers in early to middle childhood could be "a key life transition" that alters sexual development.

The next step Ellis took was to look at whether these circumstances could affect the involvement of girls in risky sexual behavior. This time he turned to Craigslist, a classified advertising Web site, and posted announcements in several cities that began, "SISTERS WANTED!" The criteria were very specific: he was looking for families with two sisters at least four years apart in age and currently between the ages of 18 and 36. He limited his search to families in which the birth parents separated or divorced when the younger sister was younger than 14 years. Ellis and his colleagues were able to recruit 101 pairs of sisters, some from families in which the parents had divorced and, using a different ad, some whose parents had not.

This time the researchers found that risky sexual behavior was not related to how long daughters lived with their fathers but to what the fathers did in the time they spent with their daughters. "Girls who grew up with a high-quality father—who spent more time as a high-investing father—showed the lowest level of risky sexual behavior," Ellis said. "Their younger sisters, who had less time with him, tended to show the highest level of risky sexual behavior."

The next question, then, is exactly how do fathers exert this effect on their daughters? One possible explanation, as unlikely as it might seem, is that a father's scent affects his daughters' behavior. Many animals emit pheromones, chemical messengers that can be picked up by others and can alter their behavior. "There is certainly evidence from animal research, in a number of species, that exposure to the pheromones of unrelated males can accelerate pubertal development and some evidence that exposure to pheromones of a father can slow it down," Ellis explained.

If the same is true of humans, pheromones could help explain how the presence or absence of fathers affects their daughters—although that remains an untested hypothesis.

father absence causes early puberty and risky behavior, then the younger daughter should show more of that behavior than her older sibling. Also, genes or the family's environment would not confuse the results, because those would be the same for both daughters. It was close to a naturally occurring experiment, Ellis realized.

Ellis recruited families with two daughters. Some were families in which the parents divorced; others were intact, to be used as a control group. He wanted to answer two questions: Was the age at which girls had their first menstrual period affected by the length of time they spent with a father in the house? And did that age vary depending on how their fathers behaved? The second question was added because fathers with a history of violence, depression, drug abuse or incarceration can affect children's development.

Ellis's suspicions were confirmed. Younger sisters in divorced families had their first periods an average of 11 months

> Although fathers matter, **others can help fill that role**. We all know children who grew up in difficult circumstances but now live rich and rewarding lives.

Some research suggests that women who sleep with a male partner have more regular menstrual cycles, perhaps because of the presence of the male's pheromones.

As we finished our conversation, Ellis brought up something I had been wondering about. What effect does father presence or absence have on sons? He told me that we do not yet know about sons. His hypothesis is that a father's involvement could have a different effect on sons, enhancing a competitive urge and spurring sons to achieve more when they grow up and leave the family.

Warts and All

As parents of teenagers understand, it is often hard to know how to respond to the crises, struggles, school challenges and social difficulties that are a normal part of the passage from childhood to adulthood. What we do *matters*—but it is so often hard to know what we should do. One key feature of good parenting, however, is to be accepting of teenagers, which again is often easier said than done—especially when they show up with a tattoo or call you from the principal's office.

Ronald P. Rohner of the University of Connecticut has spent some years looking at the consequences for children and teenagers of being either accepted or rejected by their parents. He thinks that parental acceptance influences important aspects of personality. Children who are accepted by their parents are independent and emotionally stable, have strong self-esteem and hold a positive worldview. Those who feel they were rejected show the opposite—hostility, feelings of inadequacy, instability and a negative worldview.

Rohner analyzed data from 36 studies on parental acceptance and rejection and found that they supported his theory. Both maternal and paternal acceptance were associated with these personality characteristics: A father's love and acceptance are, in this regard, at least as important as a mother's love and acceptance. That is not necessarily good news for fathers—it increases the demands on them to get this right. "The great emphasis on mothers and mothering in America has led to an inappropriate tendency to blame mothers for children's behavior problems and maladjustment when, in fact, fathers are often more implicated than mothers in the development of problems such as these," Rohner says.

Empathy is another characteristic that we hope teenagers will develop, and fathers seem to have a surprisingly important role here, too. Richard Koestner, a psychologist at McGill University, looked back at 75 men and women who had been part of a study at Yale University in the 1950s, when they were children. When Koestner and his colleagues examined all the factors in the children's lives that might have affected how empathetic they became as adults, one factor dwarfed all others—how much time their fathers spent with them. "We were amazed to find that how affectionate parents were with their children made no difference in empathy," Koestner says. "And we were astounded at how strong the father's influence was."

Melanie Horn Mallers, a psychologist at California State University, Fullerton, also found that sons who have fond memories of their fathers were more able to handle the day-to-day stresses of adulthood. Around the same time, a team at the University of Toronto put adults in a functional MRI scanner to assess their reactions to their parents' faces. Mothers' faces elicited more activity in several parts of the brain, including some associated with face processing. The faces of fathers, in contrast, elicited activity in the caudate, a structure associated with feelings of love.

The evidence shows that fathers make unique contributions to their children. It emphatically does *not* show that children in families without fathers in the home are doomed to failure or anything close to that. Although fathers matter, others can help fill that role [see "Build Your Own Family" on page 48]. We all know children who grew up in difficult circumstances but now live rich and rewarding lives. Not all of them grow up to be the president of the United States, but Barack Obama is an example of what can be achieved by a child who grew up without a father but managed to overcome it.

Fatherhood is about helping children become happy and healthy adults, at ease in the world, and prepared to become fathers (or mothers) themselves. We often say that doing what is best for our kids is the most important thing we do. The new attention to fathers, and the research we have discussed here, should help all of us find our way. M

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EYES, CAMERA, ACTION!

TO IMPROVE PHOTOGRAPHY, ENGINEERS ARE DESIGNING CAMERAS THAT

BEHAVE MORE LIKE EYES BY KLAUS M. STIEFEL AND ALEX O. HOLCOMBE

In a clearing in a subtropical rain forest in northern Australia, you can watch the light dance as it filters through the rustling canopy. Below, the leaves of the bushes form an intricate pattern of shadows on the trunks of trees. A wallaby grazes in the open space. You raise your smartphone and aim it at the tranquil marsupial. Just as you tap the button to take its picture, the wallaby notices you and hops away. In the image on your screen, half of the snapshot is too dark to make out details, and the sky between the treetops looks bleached white. The hopping wallaby is a blurry, small blob near the center of the photograph. Zooming in on the animal exposes an almost Cubist field of pixels, his outline visibly broken up into the smallest squares of the camera's sensor.

For any of us who snap photos, whether with a tap of the screen or by holding up a professional-grade piece of equipment, the experience described above—if perhaps not the wallaby—will be a familiar one. The proliferation of smartphones has turned nearly all of us into amateur shutterbugs. According to a Pew Research Center survey, more than half of all U.S. Internet users post original photos online. Instagram, the popular sharing service, reports that some 55 million pictures are posted to its network daily—that's 38,000 a minute. Yet not a single one of those millions on millions of images comes anywhere close to capturing the vivid, rich world we experience with our eyes.

None of the problems of exposure, pixelation or motion blur *ever* happens when you use your eyes. So where is the app that turns your smartphone camera into the equivalent of your eye? Engineers are now working on just that. By designing cameras that mimic the ways in which evolution has solved the image-creation problem in the brain, they hope to improve the quality of our personal photos. But there is more. With better cameras, we will have robots that can independently and smartly navigate the world and security cameras that recognize, as a human can, when a person is in trouble and can swiftly dispatch help. As we view things more and more through the eyes of computers, so, too, will our computers learn to see more like humans do.

To understand how this technological innovation is coming about, we have to first understand how the eye does its inimitable job—and where cameras fall short.

The Nature of Exposure

A glaring weakness of cameras is their inability to handle high and low lighting conditions in a single shot. In rare circumstances, our eyes also encounter this problem. When emerging from a dark basement into full sun, for example, we speak of being "blinded by the light." This transient moment, from which our eyes quickly recover, is one of the few instances in which our eyes can be said to suffer from overexposure. Historically, English did not even have a word for overexposure, because our vision has been peerless in its ability to avoid the problem. It took the invention of cameras for the concept of an inappropriately lit image to emerge.

The reason is dynamic range. It is the difference between the lowest and highest light intensity that our eyes or a camera can register. Light comes in tiny packages, called photons, that race around the universe at—you guessed it—light speed. But they do so at different energy levels. High-energy photons are perceived as blue, and those with much less energy look red. When photons collide with matter, they can get rerouted or absorbed. For example, water molecules selectively absorb low-energy photons, which is why water appears blue. A solid dark wall absorbs nearly all the photons hitting it and turns their energy into minuscule bits of heat, which explains why a wall can sometimes feel warm to the touch. More exotic materials absorb photons, and

AS WE VIEW THINGS MORE AND MORE THROUGH THE EYES OF COMPUTERS,

FAST FACTS

PICTURE PERFECT

1. Cameras encounter problems that eyes never face in producing images, such as incorrect exposure, motion blur and insufficient resolution.
2. To address these shortcomings, engineers are now designing camera technologies that mimic the human eye.
3. A retina-inspired chip, for example, could pave the way not only to better cameras but also to smarter robots.

PRECEDING PAGES: FLOREA MARIUS CATALIN *Getty Images* (*lens*); GANDEE VASAN *Getty Images* (*iris*)

Emerging from darkness into full sun is one of the rare cases when our eyes struggle with light exposure. Cameras, however, frequently produce under-exposed and over-exposed images.

instead of emitting heat, they amplify that energy into signals that are useful to cameras and brains.

In a digital camera, the photon-absorbing objects are called photodiodes. A photodiode is equivalent to a pixel, so the more photodiodes a camera has, the higher the picture's quality. This device, often made of silicon, is simply a light detector. When a photon hits it, the particle knocks an electron in the silicon to a higher energy level. The resulting charge excites the electron, causing electricity to flow. A semiconductor chip amplifies the electrical signal from every photodiode.

The brightest light a Canon 5D II—a top-of-the-line single-lens reflex camera—can discriminate is 2,000 times stronger than the weakest light it can sense. If a scene's luminance exceeds this range, overexposed and underexposed image regions occur, and photographic shame ensues. But if you had looked with your eyes instead, the same photon would have hit your retina. More precisely, it would enter a cell in your retina called a photoreceptor and excite an electron. The particle in question sits inside a retinal molecule (a form of vitamin A), which is part of a protein in the photoreceptor cell.

Tickled by the excited electron, the retinal molecule starts to twist, which in turn triggers its encompassing protein to change its configuration. This shape shifting kicks off a chain of downstream effects, involving other proteins morphing, gateways in cell membranes slamming shut, and the slowing of the flow of glutamate, an amino acid. All this squishy biological machinery amplifies the infinitesimal energy of a photon enormously, producing a signal strong enough to drive neurons.

In fact, the amplifying power of the retina is so immense that in a completely dark room, a light source need only emit about five photons for you to perceive it. To achieve this level of sensitivity, our eyes have evolved a special type of supersensitive photoreceptor dedicated to dark, nightlike conditions. These so-called rods, although they are used only in the dark, are 20 times more numerous than the cone-shaped photoreceptors we use during the day. Vision at night was apparently very important in our evolutionary history because including all those rods does not leave much room for our cone-shaped, daytime receptors.

SO, TOO, WILL OUR COMPUTERS LEARN TO SEE MORE LIKE HUMANS DO

The two kinds of photoreceptors together allow us to register an enormous range of light levels. Yet even without the nighttime receptors, our eyes operate over an incredible range. If you work late in a brightly lit office, you may look out the window wistfully as the sun sets and the trees become dark silhouettes. Yet still you can see objects outside and things inside your brightly lit office simultaneously. The range of light levels to which your eye is sensitive is so vast that it can differentiate between two objects, one of which is a million times brighter than the other.

EVGENY SERGEEV *Thinkstock*

YOUR EYE IS SO SENSITIVE TO LIGHT THAT IT CAN DIFFERENTIATE BETWEEN

During the fraction of a second that it takes for a camera's shutter to snap, this biker will have moved several centimeters. The camera's photodiodes will capture light during that entire span of time.

The advantage lies in the fact that every photoreceptor has its own exposure setting, which is constantly changing in response to the level of light received. To mimic the range of the eye, some cameras can now combine several exposures taken in quick succession. An overexposed shot provides a properly lit view of the dark parts of a scene, and an underexposed shot captures bright parts, such as the sky. Fused together, these too bright and too dark photographs produce an image with a range larger than what is possible with any individual shot. The trick fails when photographing fast-moving objects because they change position between the different exposures, but it works well for landscape photography. Even if your camera does not have a built-in high-dynamic range function, you can fuse several images post hoc on your laptop to achieve a compound image devoid of overexposed and underexposed areas.

Caught in the Act

Let's return to the hopping wallaby and why it turned out blurry. One of the problems is that a camera's shutter speed is only so fast (say, one fiftieth of a second), so a photograph will capture the light during that entire span of time, during which the wallaby's body traveled several centimeters. Our visual system is no quicker, so the image created by our photoreceptors also is blurred. Yet somehow we do not perceive much blur.

After light hits the retina, several specialized types of neurons, which connect neighboring photoreceptors, modify the light signals before sending them on to the brain. Some of these neurons react to movement in a certain direction, others to bright signals surrounded by darkness, and so on. Together they allow the eye to adjust its sensitivity.

Ultimately your visual system is most interested in change. The eyes move constantly, altering the amount of light impinging on your photoreceptors and maintaining your image of the world. If your eyes are kept still, the lack of change in a scene will cause the retina to stop signaling, and objects will begin to fade away. Swiss physician Ignaz Troxler first noticed this phenomenon in 1804. A bias toward change helps to emphasize new data over old. And it is a neat trick for overcoming the imperfections of the optical apparatus. For example, this change bias is the reason we never see the blood vessels in the eye, which sit between the outside world and our photoreceptors.

Although this trick has yet to be incorporated into consumer cameras, an experimental camera that has been developed by Tobi Delbrück of the In-

THE AUTHORS

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JANA KRIZ *Getty Images*

TWO OBJECTS, ONE OF WHICH IS A MILLION TIMES BRIGHTER THAN THE OTHER

stitute for Neuroinformatics in Zurich illustrates an extreme form of change bias. This camera's chip does not simply record the amount of light hitting every pixel, as a standard camera does, but relies on changes in the light intensity. The image that this camera creates is essentially a record of the movement and change that occurred while the picture was being taken. Pixels that increase in intensity appear white, whereas lessening intensity shows up as a black pixel. If a pixel does not change from moment to moment, the image shows only a bland gray pixel. This emphasis on change ignores stationary, unchanging objects to help isolate moving ones.

Graduate student Greg Cohen of the University of Western Sydney (a colleague of Stiefel) is working with this retina-inspired camera chip to create a robot that can play Ping-Pong, a game that is all about change and motion. In Ping-Pong, the opponent, his paddle and especially the ball move at astonishing speeds. Not all the information in a Ping-Pong scene helps in hitting the ball back across the table, such as the window behind an opponent or the patterns on the floor. The retina-inspired camera's feature of ignoring static objects helps with the task, allowing the robot to concentrate on detecting and responding to motion. Playing Ping-Pong requires such brilliant hand-eye coordination that success at this task may lead to solutions useful for a variety of applications, such as care for the elderly or search-and-rescue operations.

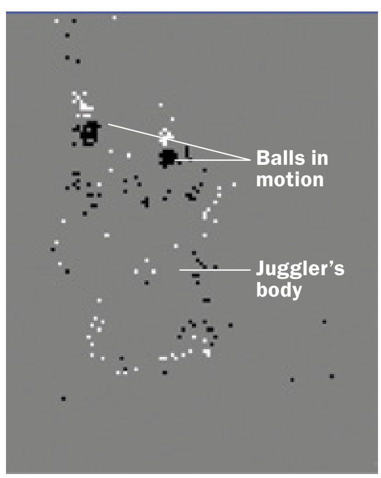
Saving Face

Although the retina takes care of the first steps in seeing, much more processing occurs in the brain. For example, we rapidly appreciate a photo when our brain can easily separate the main subject from its background. Skilled photographers know how to make that task easy for the brain, for instance, by putting one person's face in focus while limiting the depth of field so that the background is blurred. Faces are a special class of objects for us. In a busy visual scene, the human gaze will preferentially seek them out. A photograph in which they are blurred is almost always considered a ruined shot.

Several brain areas contribute to our ability to process faces. When a visual signal leaves the retina, it travels to a part of the brain called the thalamus. The thalamus is a sophisticated relay station en route to the cortex, the tightly folded mantle that makes up the brain's surface. A number of patches of cortex help us process what we see. The primary visual cortex is a large piece of real estate at the back of the brain where most signals leaving the thalamus end up. From there the information about our visual world travels to several additional visual regions of the cortex. Of these, various small areas in the temporal cortex (located on the sides of the brain) react very specifically to seeing faces.

Camera makers have begun to implement something akin to our brain's ability to recognize and prioritize faces. Many of today's cameras, even simple point-and-shoot ones, recognize faces in their field of view. This is typically done with an advanced statistical method known as the Viola-Jones algorithm. In brief, the camera's chip filters the image for basic features such as edges and corners. Region by region, it then runs a series of tests to look for facial

The Troxler illusion (*seen at left*) illustrates the way neurons cease to respond to an unchanging stimulus. Focus on the dot in the middle the circle. After several seconds, the circle will fade away. At the right, a retina-inspired camera was used to create an image of a man juggling. The dark spots in the upper part of the image are the locations that the balls are moving away from, and the white dots are the locations they are moving to.



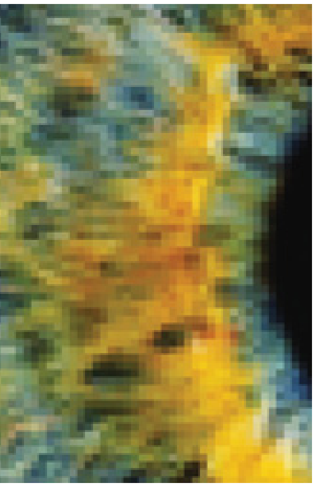
SOURCE: "THE ROLE OF FIXATIONAL EYE MOVEMENTS IN VISUAL PERCEPTION," BY SUSANA MARTINEZ-CONDE ET AL., IN *NATURE REVIEWS NEUROSCIENCE*, VOL. 5, NO. 3; MARCH 2004 (*Troxler illusion*); TOBI DELBRÜCK AND GREG COHEN (*juggler*)

To help put a face in focus, a photographer might limit the depth of field, rendering the background blurry. Cameras replicate that capability by using algorithms that search a scene for facelike features.

features. For example, it would look to see if a bright spot (a nose) occurs between two darker spots (the eyes). Only if part of the image passes all these tests does the algorithm decide that it is seeing a face. Now the camera can make sure to keep that visage in focus.

Most likely, the brain's method of processing faces differs considerably from the Viola-Jones algorithm. Hence, the face-recognition algorithm in modern cameras is not a software implementation of the brain's way of recognizing faces but rather a different solution to the same problem. By pairing such advances in image processing with knowledge about human visual preferences, we can greatly improve the photographs we produce.

Zooming in on the image on page 53 reveals the pixelation that inevitably afflicts photographs. Our visual system does not create pixelated images, because our mind has evolved to fill in the gaps.



Megapixels on the Mind

The face-selective areas of the cortex are only a small subset of the brain territory devoted to vision. Other sections of it react to different aspects of the visual scene, such as color, motion and orientation. This hubbub of activity culminates in the visual world we perceive around us.

The coordinated efforts of these brain areas are the reason why in real life you never see anything coarse-grained the way you do when you zoom in on a photo. Increasing the number of megapixels (MP) in a camera cannot solve this problem. The first digital camera Stiefel proudly owned had a 2-MP sensor, yet these days even most smartphones have at least double that. We can continue cramming in more pixels—advances in manufacturing will very likely miniaturize the hardware even further—yet it will remain the case that blowing up a smooth-seeming image will eventually transform it into a mess of boxy colors.

This limitation arises when two neighboring photons strike the same photodiode, meaning their energy will be combined into a single pixel. At that point, the information about their exact original locations is lost forever. Unfortunately, no image-processing software can create more meaningful pixels. You can scale up the size of your digital photograph, but the newly created pixels will have no new information about the light entering your camera when you pressed the shutter. Further, the scaling is not as big as you might think. The pixels of a 16-MP camera are only twice as small as a 4-MP camera. The human retina, in contrast, contains only about 6 million functioning daylight photoreceptors (cones)—just 6 MP.

In essence, our brain constructs a percept of what it evolved to regard as reality—and the human brain does not consider the graininess of the human retina a feature of external reality. What we perceive is a construction, a masterful portrait that involves much filling in between our individual sensors. There are no such things as pixels in our percepts—our brain does not to reproduce an image of light piece by piece, as if it were a biological supercamera. Rather the brain synthesizes a coherent impression for a specific purpose—that of allowing us to find our way through the world. The principle of the eye and that of the camera are fundamentally different. Unless, in a far-off future, we develop truly intelligent machines and put one in a camera body, that difference will not be bridged.

Nevertheless, the possibilities available to engineers continue to increase, together with better understanding of the eye and brain. Combining these with a little creative thinking should yield many more exciting advances in camera technology. **M**

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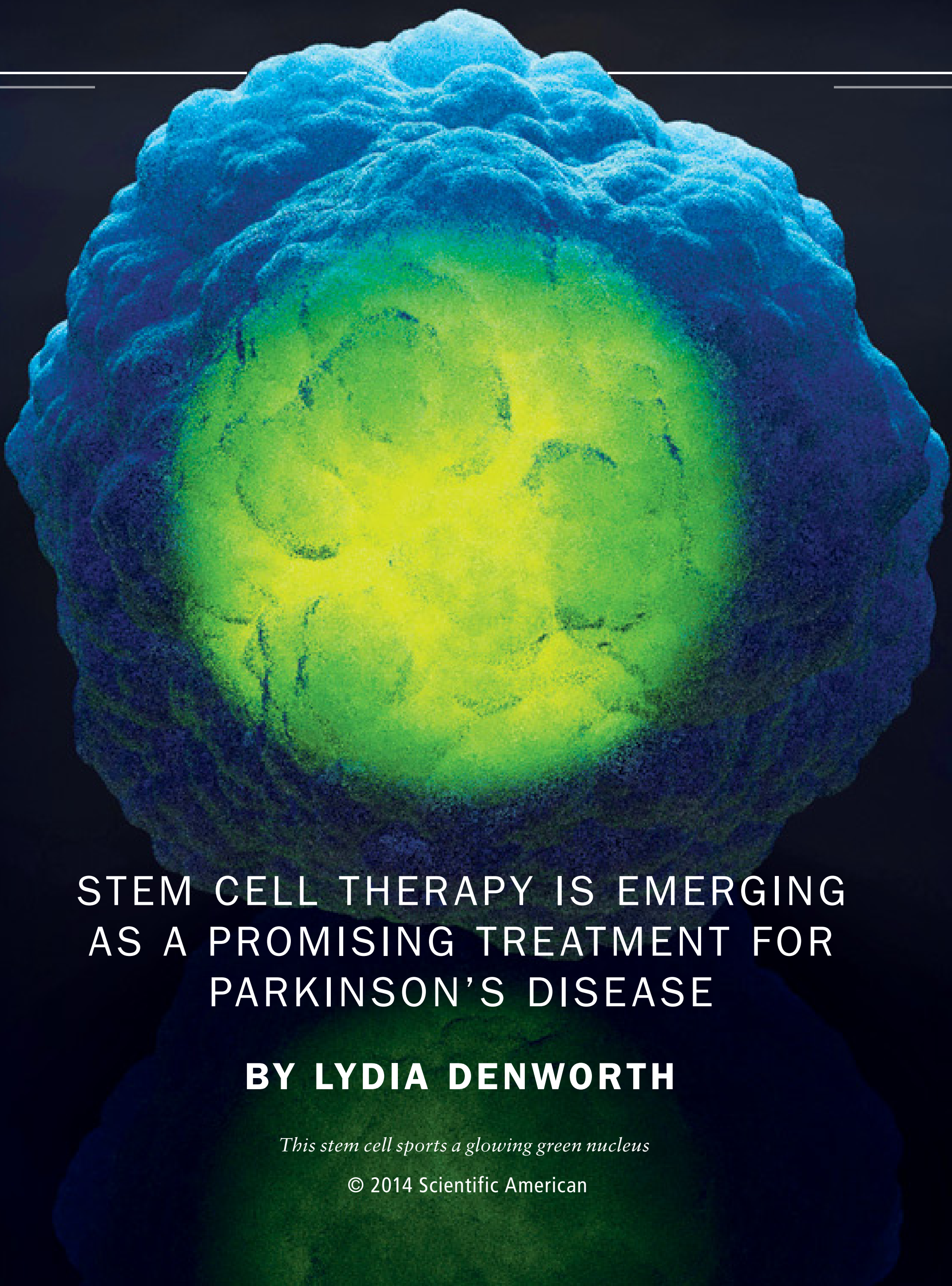
ISTOCKPHOTO (*woman*); GANDEE VASAN *Getty Images* (*iris*)

THE REGENERATING BRAIN

STEM CELL THERAPY IS EMERGING AS A PROMISING TREATMENT FOR PARKINSON'S DISEASE

BY LYDIA DENWORTH



This stem cell sports a glowing green nucleus

Neurosurgeon Ivar Mendez of the University of Saskatchewan often shows a video clip to demonstrate his work treating Parkinson's disease. It features a middle-aged man with this caption: "Off medications." The man's face has the dull stare typical of Parkinson's. Asked to lift each hand and open and close his fingers, he barely manages. He tries but fails to get up from a chair without using his hands. When he walks, it is with the slow, shuffling gait that is another hallmark of Parkinson's, a progressive neurological disorder that afflicts an estimated one million Americans, most of them older than 60.

Then the video jumps forward in time. The same man appears, still off medications. It is now eight years since Mendez transplanted dopamine cells from a fetus into the patient's brain. These neurons, which live in a midbrain region called the substantia nigra and secrete the neurotransmitter dopamine to initiate movement, are the ones that die off in Parkinson's. The man has aged, but his energy and demeanor are characteristic of a much younger man. Asked to do the same tasks, he smoothly raises his arms high and flicks his fingers open and shut rapidly. Arms crossed on his chest, he rises from a chair with apparent ease. Then he struts down the hall.

In the 25 years since the first few patients received transplants as part of a clinical trial at University Hospital in Lund, Sweden, hopes of using cell-based therapy as a treatment for Parkinson's have repeatedly risen and then been dashed. Stem cells are a biological raw material of enormous potential because they can generate new cells through the ability to divide indefinitely and to give rise to specialized cells. These cells can then be used to repair brain damage from degenerative disorders such as Parkinson's. Stem cells, however, have been hard to come by. So far the cells transplanted in humans have been derived from aborted fetal tissue, although scientists have also transplanted stem cells

In Parkinson's disease, neurons that release the neurotransmitter dopamine (*digital illustration at left*) sicken and die. After a patient loses about 70 percent of one type of dopamine neuron, tremors and muscle rigidity, among other movement problems, appear.

derived from human embryos into animals. Thorny political and ethical issues limit access to both fetal cells and embryonic stem cells, and fetal cells are in particularly short supply. Two large clinical trials using fetal tissue, published in 2001 and 2003, were considered failures because of their widely variable results; not enough patients improved by the study end points, and some developed serious side effects. Many scientists gave up on cell therapy.

But a handful of laboratories persevered. Now new evidence showing that transplantation can work well, as in Mendez's patient, and possible new sources of cells free of ethical concerns have sparked a fresh optimism. This year neurologist Roger A. Barker of the University of Cambridge will lead the first large clinical trial of cell therapy for Parkinson's in a decade. "We've broken through the old barriers," says cell biologist Ole Isacson of Harvard University.

The momentum most likely will propel cell therapies for other disorders as well. Researchers are trying to apply the technique to more than a dozen diseases, including diabetes, spinal cord injury and several forms of cancer [see "Stem Cell Repair Shop," on page 64]. In addition to Parkinson's, the most significant progress has been made with retinal diseas-

FAST FACTS

DIVIDE AND CONQUER

1. Stem cells can divide indefinitely and give rise to specialized cells, which can be used to repair brain damage from degenerative disorders such as Parkinson's.
2. Ethical concerns, limited access to stem cells and mixed results from clinical trials have stifled progress in advancing stem cell therapies; however, novel techniques for producing and transplanting these cells have recently inspired optimism.
3. Researchers are aiming to use stem cells to treat more than a dozen diseases, including diabetes, spinal cord injury and several forms of cancer.

PRECEDING PAGE: DAVID MACK *Science Source*; THIS PAGE: CAROL AND MIKE WERNER *Science Source*

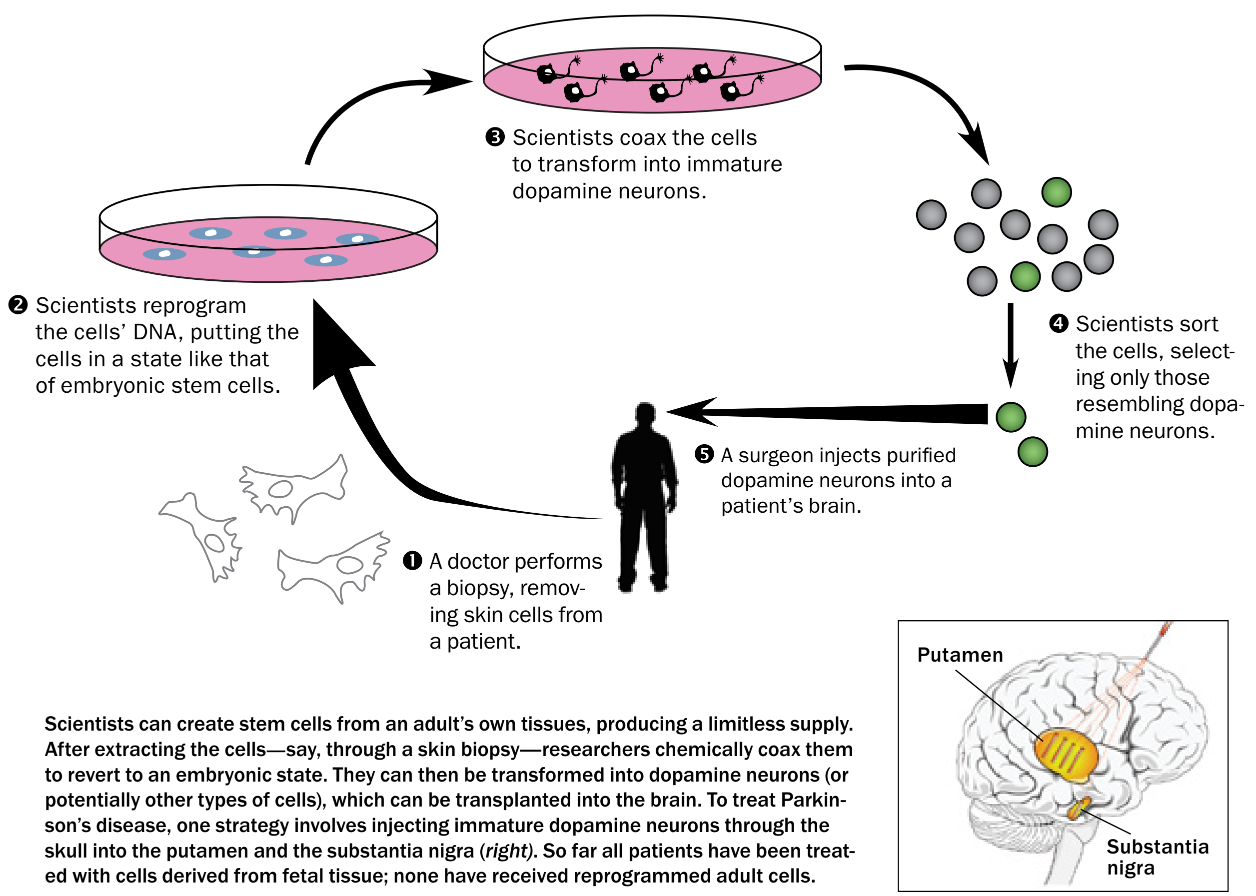
es. Clinical trials are under way to use retinal pigment epithelial cells for treatment of macular degeneration. According to the California Institute for Regenerative Medicine, theoretically there is no disease to which stem cell therapy could not be applied. In each case, the requirements depend on the difficulties inherent in generating the specific type of cell scientists hope to replace.

Progress in Parkinson's has been particularly promising, Isacson says, because "it's easier to solve." The debilitating movement difficulties characteristic of the disease have a relatively straightforward cause: dopamine loss. And researchers were able to generate dopamine neurons from stem cells quite quickly. Cell therapy typically leads to restored mobility and function—improving patients' gait, for instance, and reducing tremor—but does not ameliorate every aspect of Parkinson's. Patients may still suffer from dementia, gastrointestinal problems and sleep disorders, for instance. Yet in the best-case scenario, patients could gain 20 to 30 years of excellent quality of life with a single intervention and require virtually no medications. "You've not cured the disease," Barker says, "but you've transformed the natural history of Parkinson's disease."

Delivering Dopamine

A mild tremor in the hand or some other extremity is often the first sign of Parkinson's. Tremors are followed by rigidity in the muscles, a stooped posture and the distinctive difficulty walking first described by James Parkinson in 1817. The movement difficulties relate to the loss of a dopamine neuron called A9 in the substantia nigra, which among other things controls the initiation of mo-

REPLACING LOST NEURONS



Scientists can create stem cells from an adult's own tissues, producing a limitless supply. After extracting the cells—say, through a skin biopsy—researchers chemically coax them to revert to an embryonic state. They can then be transformed into dopamine neurons (or potentially other types of cells), which can be transplanted into the brain. To treat Parkinson's disease, one strategy involves injecting immature dopamine neurons through the skull into the putamen and the substantia nigra (*right*). So far all patients have been treated with cells derived from fetal tissue; none have received reprogrammed adult cells.

SCIENTIFIC AMERICAN MIND; SOURCE: IVAR MENDEZ *University of Saskatchewan* AND OLE ISACSON *Harvard University*; ISTOCKPHOTO (*man*); IVAR MENDEZ (*brain inset*) tion. By the time the first tremor appears, patients have already lost about 70 percent of those A9 neurons—a threshold that is like a water level, Isacson says. They hit the water and begin to sink under a flood of movement troubles.

Since the 1960s Parkinson's has been treated with medications that replace missing dopamine in the brain. L-Dopa is a dopamine precursor, and doses of this small molecule cross the blood-brain barrier and enter brain cells, which convert L-Dopa into dopamine and release it. Other drugs, known as dopamine agonists, stimulate dopamine receptors in the absence of the neurotransmitter, thereby mimicking its effects. The medications improve parkinsonian symptoms, but their benefits diminish over time, and they carry side effects such as alternating periods of mobility and immobility and the emergence of additional jerky movements.

In the 1990s clinicians developed an alternative therapy called deep-brain stimulation (DBS), the surgical insertion of an electrode that delivers electrical pulses to directly alter neuronal activity in a specific area of the brain. The treatment can work well. At the University of California, San Francisco, Medical Center, for example, 45 to 70 percent of patients who receive DBS for Parkinson's improve. Yet over time, patients begin to decline again because the electrode stimulation can no longer compensate for the continuing loss of dopamine. Cell-based therapy, in contrast, is designed to directly restore the cells lost in the disease process.

The earlier large clinical trials of cell therapy suffered from multiple problems. For example, it now appears that some of the patients selected were too old and their disease too advanced to get good results. Instead of infusing a substance containing a single type of cell, surgeons transplanted chunks of tissue, which included other material that triggered immune reactions. The procedure itself was conducted differently by every team. Moreover, the end points for the studies were too short—neither was more than two years—for the transplanted cells to take full effect.

Of the patients who have received cell-based therapy for Parkinson's, those transplanted by Mendez's team have done best. Mendez began transplanting fetal cells into patients in the late 1990s, when he was at Dalhousie University in Nova Scotia. He improved the preparation of the cells by treating them to encourage growth and creating pure cell suspensions instead of transplanting chunks of tissue. Using a computerized injector that he developed to standardize the process, Mendez targeted two brain areas instead of one—the substantia nigra, where dopamine cells naturally originate, and the putamen, which their axons need to reach. All 10 of his patients improved significantly on the standard Parkinson's rating scale, which measures the course of the disease. In a separate postmortem analysis of five patients published in 2008, Mendez and Isacson, who have been collaborating for about 10 years, found that the grafted neurons survived without signs of degeneration for as long as 14 years. "Methods matter," Mendez says. "We now have all the experience and the techniques and the instruments that will be able to plant these cells safely into the human brain."

STILL, FETAL CELLS "ARE NOT THE ANSWER," ONE NEUROSURGEON SAYS. POLITICS ASIDE, THERE WILL NEVER BE ENOUGH FOR ALL THE PATIENTS WHO WOULD NEED THEM.

New Kinds of Cells

The biggest remaining challenge is obtaining enough viable stem cells. The fetal cells implanted to date have been harvested from the midbrain of an aborted fetus aged six to nine weeks. Such stem cells have already differentiated into dopamine neurons yet retain the capacity to generate more new neurons after transplantation. Still, fetal cells "are not the answer," Mendez acknowledges. Politics aside, there will never be enough for all the patients who would need them.

Another possibility emerged in 1998, when cell

THE AUTHOR

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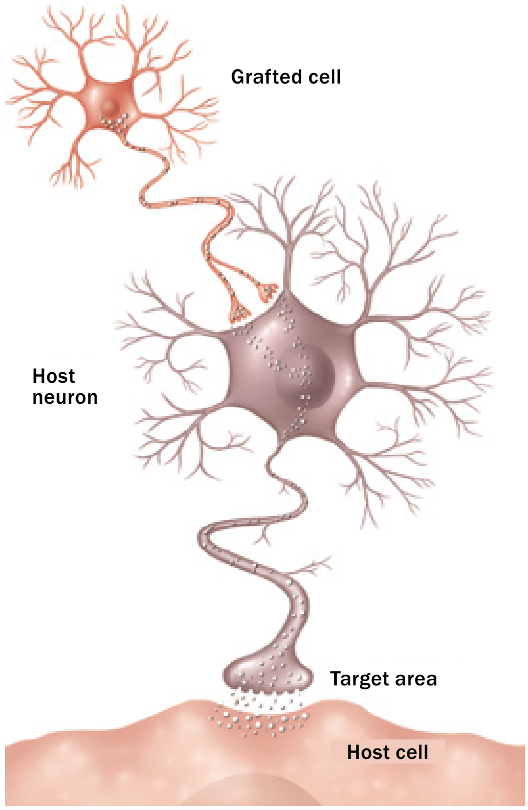
biologist James A. Thomson of the University of Wisconsin–Madison and his colleagues derived the first embryonic stem cell line. They were working with the blastocyst of a human embryo, a brief early developmental stage when the ball of cells contains an inner clump of 20 to 30 cells that are capable of growing into any of the more than 200 types of adult cells in the body. Unlike fetal tissue cells that have started down the path to differentiation, these so-called pluripotent stem cells have the potential to produce any type of tissue in the body.

Thomson's team removed those cells and nurtured them in the lab so that they divided. The result was an infinitely renewable lab-maintained source of stem cells—a cell line—that would not require further new embryos. The ethics were still complicated by the original use of embryos, but suddenly large-scale cell-based therapy seemed achievable. The challenge was to coax those embryonic stem cells to develop into the specific cells needed to treat a disease—dopamine neurons for Parkinson's, for instance, or insulin-producing cells for diabetes.

Also in 1998 Isacson's group reported that it had done just that in mice. The researchers differentiated A9 neurons from mouse blastocysts. When they injected those cells into a mouse brain, they found that the cells lived and formed connections with the other neurons in the brain. In 2002 his group showed that the same procedure restored movement and mobility in a rat with a drug-induced version of Parkinson's. Several other groups achieved similar recovery in rodents. Immediately researchers tried to create A9 neurons from human embryonic stem cells—but that step proved more difficult. "For nearly 10 years that was largely a failure," says cell biologist Lorenz Studer of the Memorial Sloan Kettering Cancer Center. "We would have expected the cells to behave well, but they did not."

A breakthrough with an alternative approach came in 2007, when the team of biologist Shinya Yamanaka of Kyoto University in Japan figured out how to create stem cells from an adult's own tissues. Beginning with adult mouse skin cells, Yamanaka's team "reprogrammed" the cells biochemically, driving them back to something resembling an embryonic stem cell, which could then be used as a basis for deriving a totally different kind of body cell, such as a neuron.

In essence, Yamanaka's group had found a way to create a limitless supply of stem cells from adult skin cells, thereby sidestepping the political and ethical issues that surround research with embryos. The accomplishment won Yamanaka the 2012 Nobel Prize in Physiology or Medicine. Furthermore, if the



When a neuron (*red*) derived from a stem cell is injected into the brain, the cell grows and connects with existing neurons (*purple*). The ability of cell transplants to integrate with established brain circuitry is essential to restoring function.

IVAR MENDEZ

cells, which are called induced pluripotent stem cells, always originate with the individual patient being treated, the considerable risk of immune rejection would disappear. "They solved a very big problem," says Mahendra Rao, director of the National Institutes of Health's Center for Regenerative Medicine.

Newly Nimble Monkeys

A year after Yamanaka's discovery, Isacson's team showed that it could create A9 dopamine neurons from such reprogrammed adult rodent cells. The scientists soon began putting the new cells in mice and rats with signs of Parkinson's, and in 2008 they reported improved function. Then they turned to nonhuman primates. Working with a monkey with drug-induced Parkinson's, Isacson's group harvested the monkey's skin cells, drove them back to an embryonic state, then differentiated them into dopamine neurons and put them into the monkey's brain. For two years, they monitored the monkey. In results presented at conferences late in 2013, they showed that according to PET scans the grafted dopamine neurons had survived and grown. About eight months after the transplant, the monkey's mo-

STEM CELL REPAIR SHOP

For decades researchers have explored the use of cells as a tool for treating a wide range of disorders. Despite its promise, stem cell repair of the body remains experimental. The following is a snapshot of progress in bringing such therapy into practice for five pressing medical conditions. *—Roni Jacobson*

CONDITION	PATHOLOGY	STEM CELL APPROACH	RESEARCH STAGE
Amyotrophic lateral sclerosis (ALS)/Lou Gehrig's disease	Cells in the brain and spinal cord that control movement die off, leading to paralysis	Transforming stem cells into new neural support cells could protect motor neurons from further destruction	Transplanted cells appeared to slow disease progression in patients with early-stage ALS; the preliminary finding in 2012 emerged from a clinical trial meant to assess safety
Brain cancer	A type of brain tumor called a high-grade glioma is hard to treat because the blood-brain barrier prevents cancer drugs from reaching it	Neural stem cells could home in on the malignant brain cells to deliver cancer-killing agents without damaging healthy tissue	Safety trials in humans began in 2010. So far researchers have seen no adverse effects and hope to begin trials next year to establish the optimal dose
Multiple sclerosis	Inflammation in the brain and spinal cord damages myelin, a material that surrounds nerve cells and enables them to transmit signals effectively	Stem cells harvested from a patient's own bone marrow could be used to generate a whole new immune system; alternatively, engineered cells could replenish myelin	In 2013 the FDA approved the first U.S. clinical trial to test the safety of injecting stem cells into the cerebrospinal fluid of 20 patients
Spinal cord injury	Nerve fibers in the brain and spinal cord are damaged or severed, leading to complete or partial paralysis	Stem cells could stimulate and guide the growth of severed nerve fibers, although extensive scar tissue can impede regeneration	Researchers are recruiting patients for a safety trial to be completed in 2016
Type 1 diabetes	The body's immune system attacks and destroys the cells in the pancreas that produce insulin	Embryonic stem cells that mature into insulin-producing cells could replace missing pancreatic tissue	In 2012 researchers reported curing diabetes in mice using a stem cell method. They are applying to the FDA to start human trials

tor disorder ceased. A postmortem analysis showed that the new neurons had made connections with other neurons throughout the brain area where they had been grafted.

The same year two other groups also reported success with adult-derived stem cells and monkeys, including the lab of cell biologist Su-Chun Zhang of the University of Wisconsin–Madison and Yamanaka and his colleague Jun Takahashi. "All three groups now demonstrate pretty unequivocally that the graft can survive, can differentiate into the right type of cells and then can integrate into the brain structurally," Zhang says.

Isacson's monkey is the only one to be observed for a longer period—two years—and to have shown functional recovery. The researchers are pursuing longer-term studies with more monkeys to convincingly show both safety and efficacy. Clinical trials could follow, possibly within a few years, say Mendez and Isacson, who are convinced that these adult-derived cells are the future.

Others are still betting on embryonic stem cells. In 2011 Studer's lab successfully differentiated human embryonic stem cells into dopamine neurons. When grafted into a mouse, rat or monkey with parkinsonian symptoms, these cells now survive and lead to recovery of function. Studer recently received a $15-million grant to perfect his technique and generate cell lines based on GMP (good manufacturing practice) guidelines. "Now we have a protocol that led us to say we might actually be ready," Studer says. In parallel with the work manufacturing large batches of cells, he plans to begin lining up patients for a clinical trial, most likely the first to use embryonic stem cells.

One reason for sticking with embryonic stem cells is regulatory. "This is all new ground," says University of Cambridge's Barker. "Cells are not a drug, and they are not a device. What are they?" To date, stem cells have been regulated by line—a set of renewable cells that are cultured in one lab and deemed safe. If stem cells are produced for individual patients—using the full potential of the newest technology—and still are required to follow the same approval process as existing stem cell lines, the therapy would be cost-prohibitive. One solution is to approve a generic induced stem cell process rather than separate lines. Another answer, which sacrifices some immune response benefits, would be to create a bank of up to as many as 500 regulated stem cell lines derived from adult tissue, which could, Isacson says, be genetically matched to 75 to 90 percent of the population.

Revolutionary Treatment

In his upcoming trial, Barker's team of collaborators will implant stem cells into the brains of 20 patients in Europe and follow 130 other patients whose Parkinson's is progressing naturally. Learning from past procedural mistakes, the scientists are still using fetal tissue but have tightened the selection of patients, improved tissue preparation and placement, and rethought the length and follow-up for the multicenter trial. The TransEuro study is intended to provide proof of the principle that cell therapy can consistently repair the brain, Barker says. "The importance is the process, which we see as the stepping-stone to the next generation of cell-based therapies."

THE GRAFTED NEURONS HAD SURVIVED AND GROWN IN THE MONKEY'S BRAIN. ABOUT EIGHT MONTHS AFTER THE TRANSPLANT, THE MONKEY'S MOTOR DISORDER CEASED.

Despite its theoretical superiority, populating the brain with new dopamine cells is not yet obviously better than existing treatments such as DBS, which brings faster results. In addition, other treatments in development may prove feasible. For example, in early 2014 researchers at Imperial College London reported promising results from the first gene therapy trials for Parkinson's patients. In this treatment, doctors insert genes for dopamine-producing enzymes into the striatum, a part of the midbrain that contributes to movement control.

Many researchers believe, however, that the remaining hurdles in producing and validating stem cell therapy can be cleared for Parkinson's. To Rao, who in his post at the NIH oversees all the work under way in regenerative medicine, the progress so far has been encouraging. "These are the first steps in what could be a revolutionary treatment," he says. **M**

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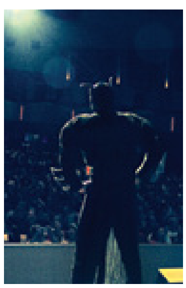
WHAT A TRIP

Take a visual journey through seven prizewinning illusions

By Stephen L. Macknik and Susana Martinez-Conde

STEPHEN L. MACKNIK and SUSANA MARTINEZ-CONDE are laboratory directors at the Barrow Neurological Institute in Phoenix. They serve on *Scientific American Mind*'s board of advisers and are authors of *Sleights of Mind: What the Neuroscience of Magic Reveals about Our Everyday Deceptions,* with Sandra Blakeslee, which recently won the Prisma Prize for Best Science Book of the Year (http://sleightsofmind.com). Their forthcoming book, *Champions of Illusion,* will be published by Scientific American/Farrar, Straus and Giroux.



Decked out in a mask, cape and black spandex, a fit young man leaps onto the stage, one hand raised high, and bellows, "I am Japaneeeese Bat-Maaaaaan!" in a thick accent. The performer is neither actor nor acrobat. He is a mathematician named Jun Ono, hailing from Meiji University in Japan. Ono's single bound, front and center, at the Philharmonic Center for the Arts in Naples, Fla. (now called Artis-Naples), was the opening act of the ninth Best Illusion of the Year Contest, held May 13, 2013. Four words into the event, we knew Ono had won.

Aside from showcasing new science, the contest celebrates our brain's wonderful and mistaken sense that we can accurately see, smell, hear, taste and touch the world around us. In reality, accuracy is not the brain's forte, as the illusion creators competing each year will attest. Yes, there is a real world out there, and you do perceive (some of) the events that occur around you, but you have *never actually lived in reality*. Instead your brain gathers pieces of data from your sen-

SIMONE GORI (*contestants and inset*); VICTORIA SKYE (*Batman*)

sory systems—some of which are quite subjective or frankly wrong—and builds a simulation of the world.

This simulation, which some call consciousness, becomes the universe in which you live. It is the only thing you have ever perceived. Your brain uses incomplete and flawed information to build this mental model and relies on quirky neural algorithms to often—but not always—obviate the flaws. Let us take a spin through some of the world's top illusions and their contributions to the science of perception. (To see videos of these illusions, see **ScientificAmerican.com/may2014/illusions**.)

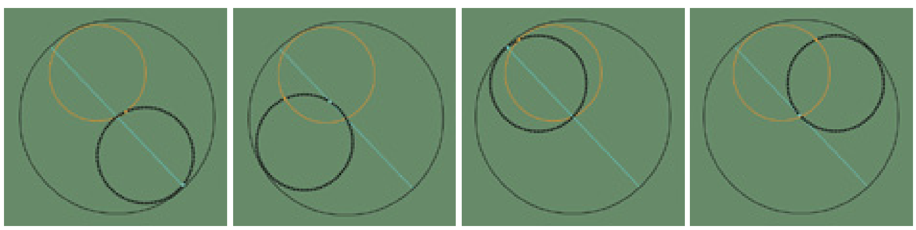
JUN ONO, AKIYASU TOMOEDA AND KOKICHI SUGIHARA *(top)*; ARTHUR SHAPIRO AND ALEX ROSE-HENIG *(bottom)*

TRANSLATION WITH A TWIST

A famous proof by Swiss mathematician Leonhard Euler indicates that if you move a rigid body so that only a single point on that body remains fixed, you will have achieved rotation. As mathematicians of the mind, Ono and his colleagues Akiyasu Tomoeda and Kokichi Sugihara did not need Euler's theorem to create the *illusion* of rotation.

Ono, Tomoeda and Sugihara showed that moving certain static figures across a grid pattern causes us to perceive rotation where none exists. Two identical stationary pinwheels seem to spin in *opposite directions* when a grid moves across them. This illusion tells us that the motion we perceive emerges from the interaction between an object's actual motion and contextual information in its background and foreground. Given that everyday objects almost never move in front of an undifferentiated background, you might not be seeing real-world motion as correctly as you think.

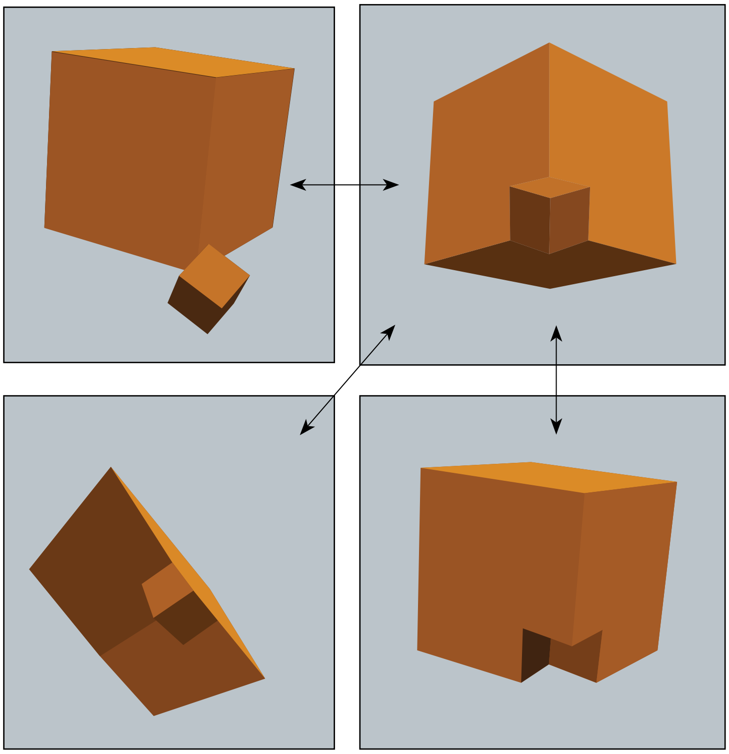
TUSI OR NOT TUSI? THAT IS THE QUESTION ...



Nasir al-Din Tusi, the 13th-century Persian astronomer, mathematically proved that the circular motion of objects, such as gears, could lead to movement in a straight line. Vision scientist Arthur Shapiro of American University and his student Alex Rose-Henig showed why we sometimes perceive straight-line motion from rotation. In their illusion, which won second prize, they use the fact that we group individual moving objects into global structures depending on the statistical relation among those objects. For instance, a set of elements that moves along a straight line or in a circle can look as if it moves in either circular or linear fashion, depending on the phase of the elements—that is, the relative time at which each begins and ends its path. The perception of linear or circular motion can also depend on what you pay attention to, and the effect can be similarly counterintuitive. The illustration above depicts a black circle in various locations as it circumnavigates the interior of a larger one. The blue dot, which sits on the smaller circle, traverses a linear path (*blue line*) as the circle moves. If you focus on that spot, however, the black circle appears to spin. The orange dot on the same circle takes a circular route (*orange path*). But if you zoom in on it, the circle's motion will look linear.

FAST FACTS
ILLUSION OF REALITY

1. You have never lived in reality. Instead your brain gathers bits and pieces of data from your sensory systems and builds a virtual simulation of the world.
2. One groundbreaking new illusion exploits the fact that our perception of motion emerges from the interaction between an object's actual motion and its background.
3. The Best Illusion of the Year Contest brings scientific and popular attention to perceptual oddities. Anyone can submit an illusion to next year's contest at **http://illusionoftheyear.com/submission-instructions for the rules**



TRIPLE VISION

We have all seen ambiguous figures in which the same object can be seen in two different ways. One example is the venerable Necker cube. Neuroscientists use such visual stimuli in experiments to help find the circuits in the brain responsible for conscious perception. They reason that our shifting perspective on ambiguous figures is based on changes in neural activity that do not correspond to alterations in the physical image cast on your retina. Thus, a modulation of the neural response under these conditions may underlie perception that is divorced from reality.

Vision scientists Guy Wallis and David Lloyd of the University of Queensland in Australia noticed that some ambiguous figures could be seen three ways, as demonstrated in their uncanny threefold cubes illusion. In this case, the illusionists made a computer model of three different objects that all looked exactly the same when seen from one critical perspective (*upper right image*). From that view, each figure is ambiguous. The brain cannot decide whether the edges are pointing toward or away from the viewer because both interpretations are equally correct. As a result, the brain cycles between the interpretations. The object could be two cubes (*upper left image*), a single cube with a cube-shaped bite out of it (*lower right image*), or a concave surface illuminated from below (*lower left image*). The illusionists then rotated each object to show that when viewed from other perspectives, the figures are clearly distinct. Each one of them represents one of the three possible visual interpretations of the item from the ambiguous perspective.

THE CASE OF PETER AND SOME KNOBBY BALLS

Illusions are not just for the visual system. They also happen in the sense of touch, as noticed by cognitive neuroscientist Peter Tse of Dartmouth College. Squeezing a ball after pinching his pencil, Tse felt that something was amiss. Try it yourself at home. Get a pencil and a small, round hard sphere, such as a ball bearing or a marble. First, squeeze the pencil lengthwise very tightly between your thumb and first finger for 60 seconds or so, until you make a deep indentation in the skin. Now feel the ball bearing at the location of the indentation by rolling it around. The ball no longer seems round but instead feels as if it has rounded corners, as if the ball were hexagonal in cross section. When you are squeezing the pencil, the array of touch receptors in your skin takes on the shape of the pencil. Yet the brain assumes that your finger's sheet of skin receptors is smooth and round, and it misattributes the perceived edges to the ball.

NO SMOKE OR MIRRORS

Clinical psychologists Sidney Pratt, Martha Sanchez and Karla Rovira of Sin Humo (a treatment program meaning "without smoke") in Costa Rica described an unusual top-10 illusion at the contest gala: they made pleasure disappear by blocking vision. Their idea came about after finding that a relaxation technique that involved closing the eyes while smoking could decrease the enjoyment people felt from a cigarette. Less enjoyment, they reasoned, would lead to weaker addiction. Pratt's team then wondered whether the patients' reduced gratification resulted primarily from the closing of the eyes—which prevented them from seeing the burning cigarette—rather than from relaxation per se.

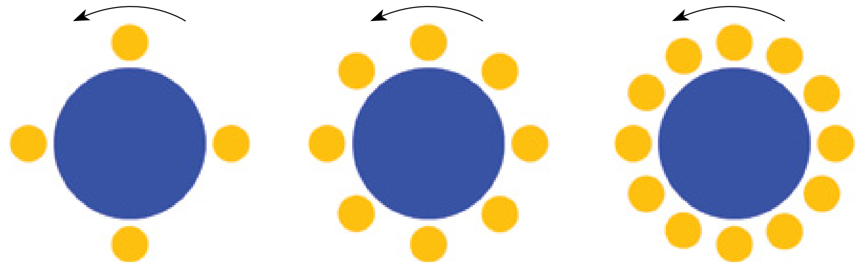
To test this idea, they simply blindfolded patients while they smoked—and found that this manipulation accounted for the reduced pleasure of smoking. The contest judges classified this demonstration as an illusion because the smokers' perceptions did not match the biochemical reality of smoking, in which the amount of pleasure from a cigarette should be based on the amount of nicotine delivered. That amount, however, is the same with and without the blindfold.

In light of this effect, the researchers reasoned that seeing the smoke from a cigarette, along with its presumed association with smoking satisfaction in the past, might bolster nicotine addiction among smokers. The blindfolding technique is now the cornerstone of the team's antismoking treatment plan.

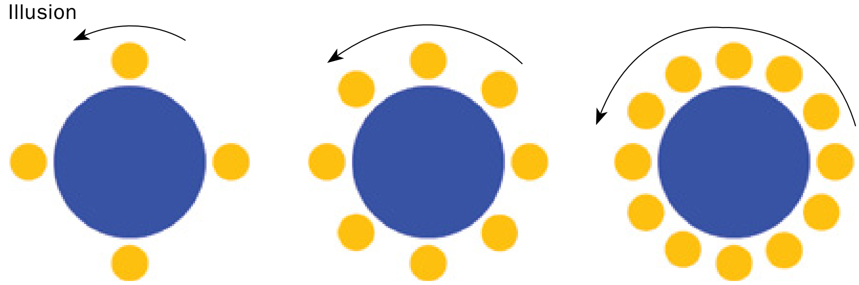
GUY WALLIS AND DAVID LLOYD (*top*); THINKSTOCK (*pencil*); ISTOCKPHOTO (*blindfold and ball*)

MORE LEGS MOVE FASTER?

Reality



Illusion

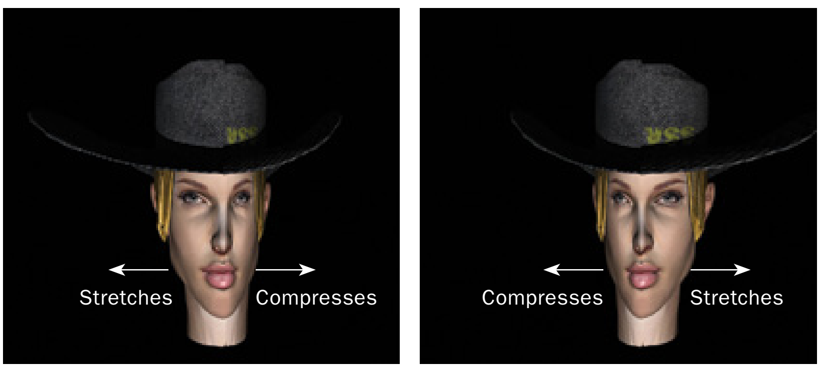


While working on a motion perception project, Alan Ho of Ambrose University College in Calgary noticed that a computer representation of a turning fan blade appeared to spin twice as fast after he doubled its number of blades. To achieve the same effect, cartoon animators draw multiple legs and feet on fast-moving characters such as Wile E. Coyote. In their coyote illusion, Ho and Stuart Anstis of the University of California, San Diego, demonstrated this principle more generally by showing that increasing the number of circles orbiting a larger circle creates the perception of faster motion even when the circles' speed remains constant.

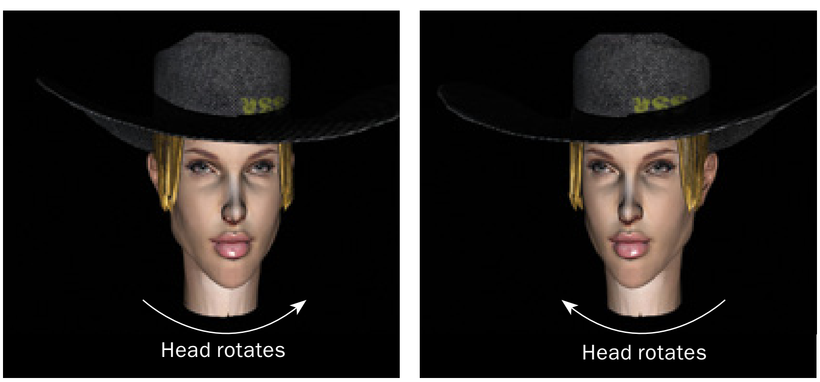
The visual system can track only the movement of slow, widely spaced spots. As the spots speed up or come closer together, they tend to blur or fuse perceptually. In such cases, Ho and Anstis showed, the brain uses a different strategy to compute velocity. Instead of tracking each moving element, the brain calculates the change of the stimulus over time at each position around the loop. That is, it simply counts the number of flickers it detects at each point in space. As a result, doubling the number of fast-moving elements means the brain sees twice as many flickers and concludes that the speed has doubled.

This illusion has commercial and practical applications. Programmers could use it to create the perception of rapid action in computer games, and advertisers might add flashing lights to billboards when they wanted viewers to perceive faster motion. Their discovery also has implications for road safety. When you are driving on a highway, roadside trees, fence poles and guardrails that are planted close together may lead you to think you are moving faster than you are.

Reality



Illusion



ALAN HO AND STUART ANSTIS (*top*); ATTILA FARKAS AND ALEN HAJNAL (*bottom*)

STRETCHING THE TRUTH

Rigid objects—or those that we *expect* to be rigid—appear to rotate when they are stretched asymmetrically. In a dramatic example, created by psychologists Attila Farkas and Alen Hajnal of the University of Southern Mississippi, a stationary computer-generated head appeared to turn when its two halves were simply stretched—but not actually rotated.

FURTHER READING

- Find all the winners of the Best Illusion of the Year Contest: **http://illusionoftheyear.com**
- Alan Ho talks about his speed illusion: **https://ambrose.edu/news_and_events/dr-alan-ho-finalist-best-illusion-year-competition**

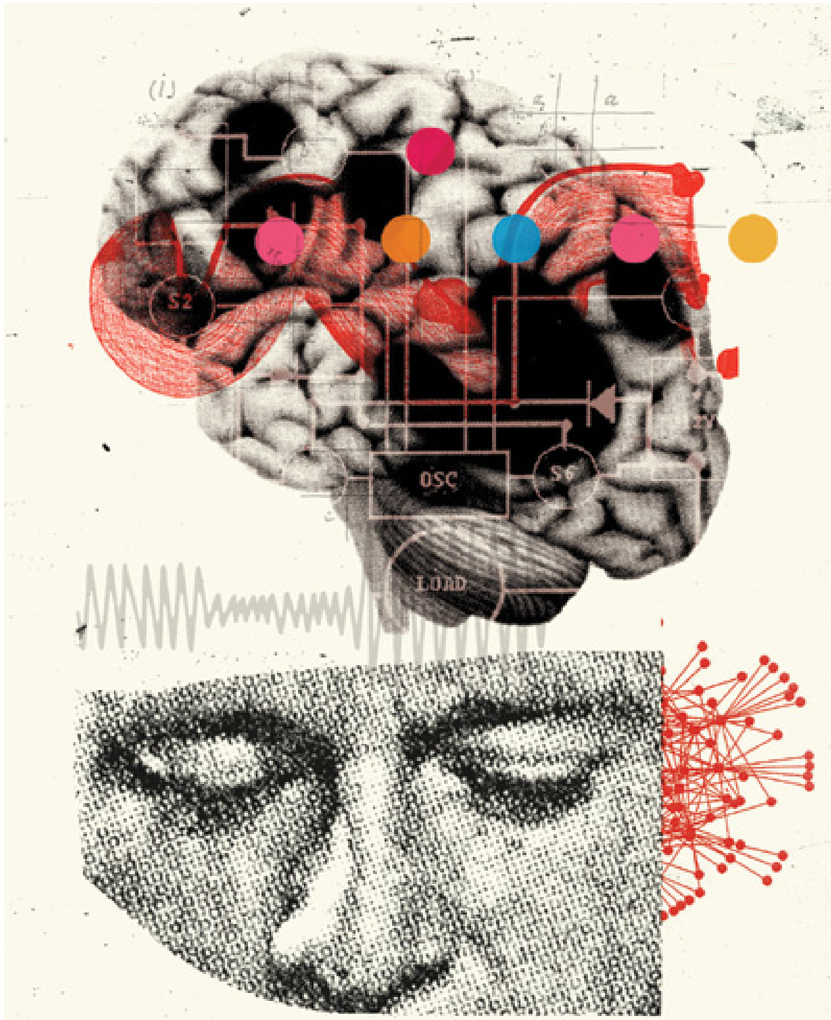
From Our Archives

- **169 Best Illusions.** Scientific American Mind Special Issue; Summer 2010.
- **10 Top Illusions.** Susana Martinez-Conde and Stephen L. Macknik; May/June 2011.
- **187 Illusions: How They Twist Your Brain.** Scientific American Special Collector's Edition; September 2013.

REMEDIES

The Truth about Shock Therapy

Electroconvulsive therapy is a reasonably safe solution for some severe mental illnesses



A rabble-rousing patient on a psychiatric ward is brought into a room and strapped to a gurney. He is being punished for his defiance of the head nurse's sadistic authority. As he lies fully awake, the psychiatrist and other staff members place electrodes on both sides of his head and pass a quick jolt of electricity between them. Several orderlies hold the patient down while he grimaces in pain, thrashes uncontrollably and lapses into a stupor.

This scene from the 1975 Academy Award–winning film *One Flew Over the Cuckoo's Nest,* starring Jack Nicholson as the rebellious patient, has probably shaped the general public's perceptions of electroconvulsive therapy (ECT) far more than any scientific description. As a result, many laypeople regard ECT as a hazardous, even barbaric, procedure. Yet most data suggest that when properly administered, ECT is a relatively safe and often beneficial last-resort treatment for severe depression, among other forms of mental illness.

Cuckoo Conceptions

One Flew Over the Cuckoo's Nest is far from the only negative portrayal of ECT in popular culture. In a 2001 survey of 24 films featuring the technique, psychiatrists Andrew McDonald of the University of Sydney and Garry Walter of Northern Sydney Central Coast Health of New South Wales reported that the depictions of ECT are usually pejorative and inaccurate. In most cases, ECT is delivered without patients' consent and often as retribution for disobedience. The treatment is typically applied to fully conscious and terrified patients. Following the shocks, patients generally lapse into incoherence or a zombielike state. In six films, patients become markedly worse or die.

Probably as a result of such portrayals, the general public holds negative attitudes toward ECT. In a 2012 survey of 165 students in undergraduate psychology courses, who are presumably more likely than most to be informed about mental illness therapies, psychologists Annette Taylor and Patricia Kowalski of the University of San Diego found that

BY SCOTT O. LILIENFELD AND HAL ARKOWITZ

Scott O. Lilienfeld and Hal Arkowitz serve on the board of advisers for *Scientific American Mind.* Lilienfeld is a psychology professor at Emory University, and Arkowitz is an associate professor of psychology at the University of Arizona.

Send suggestions for column topics to ***editors@SciAmMind.com***

ALEX WILLIAMSON (*illustration*); SEAN McCABE (*Lilienfeld and Arkowitz*) roughly 74 percent agreed that ECT is physically dangerous. And a 2006 survey of 1,737 Swiss citizens led by psychologist Christoph Lauber, then at the Psychiatric University Hospital in Zurich, revealed that 57 percent perceived ECT as harmful; only 1.2 percent supported its use.

Minimal Risk

ECT, colloquially called "shock therapy," was introduced in 1938 by Italian neurologists Ugo Cerletti and Lucio Bini as a treatment for psychosis. (Cerletti apparently got the idea after observing that cows that had been shocked prior to slaughter became sedated.) The treatment is simple: electrodes are attached to a patient's head, and electric current is passed between them, causing changes in brain chemistry and activity.

In line with the public's perceptions, the intervention often was perilous before the mid-1950s. Back then, patients were awake during ECT. The shocks caused convulsions, and broken bones were a fairly common result of the body thrashing about. After all, when properly administered, ECT induces a seizure; indeed, many researchers argue that a seizure is needed for the procedure to work.

Nowadays in the U.S. and other Western countries, patients receive ECT in conjunction with a muscle relaxant and a general anesthetic, both given largely to tamp down muscular activity during the seizure and decrease overall discomfort. Hence, although patients still undergo a seizure, they are unconscious during the procedure and do not experience pain or observable convulsions. During ECT, the patient's brain waves, along with other vital signs, are monitored to ensure safety.

These advances have made ECT much safer and less frightening than it once was. In a 1986 survey of 166 patients who had received ECT, psychiatrists C.P.L. Freeman and R. E. Kendell of the University of Edinburgh found that 68 percent reported that the experience was no more upsetting than a visit to the dentist. For the others, ECT was more unpleasant than dentistry, but it was not painful.

Still, the treatment is not hazard-free. In some countries, physicians deliver ECT much as they did in the pre-1950s era. In a 2010 review psychiatrist Worrawat Chanpattana of Samitivej Srinakarin Hospital in Bangkok and his colleagues found that 56 percent of patients across 14 Asian countries received ECT with no muscle relaxant or anesthetic. And ECT performed anywhere has some downsides. Patients typically emerge from a session temporarily disoriented. More seriously, most patients experience retrograde amnesia afterward: they no longer remember many events that occurred a few weeks to months before the treatment. The loss is less pronounced when electrodes are placed on one side of the head rather than on both. And recent technologies, including brief-pulse machines that permit the electricity doses to be carefully calibrated, minimize the extent of the amnesia. But some memory problems virtually always accompany the procedure. In addition, some studies hint that ECT can in rare cases lead to lasting cognitive deficits beyond the limited retrograde amnesia, although the data backing this possible outcome are far from definitive.

> IN ONE SURVEY, 68 PERCENT REPORTED THAT THE EXPERIENCE WAS NO MORE UPSETTING **THAN A VISIT TO THE DENTIST.**

Mysterious Mechanisms

Given its adverse effects on memory, patients should consider ECT only after other treatments have failed. Yet the bulk of research suggests that ECT can be effective at alleviating the symptoms of several mental illnesses, including severe depression and the manic phase of bipolar disorder. It also seems to ease catatonia, a condition marked by striking movement abnormalities, such as remaining in a fetal position or gesturing repeatedly, that may accompany schizophrenia and bipolar disorder.

The case for the intervention would be even stronger if researchers could determine why it works. According to a 2011 review, psychiatrist Tom Bolwig of Copenhagen University Hospital noted that ECT increases the secretion of certain hormones that are disturbed in depression. Others have suggested that the electricity stimulates neural growth and helps to rebuild brain areas that are protective against depression. A third idea is that the seizures themselves fundamentally reset brain activity in ways that often bring relief, Bolwig concludes.

ECT may also ameliorate illness by altering the sensitivity of receptors for neurotransmitters, such as serotonin [see "Is Depression Just Bad Chemistry?" by Hal Arkowitz and Scott O. Lilienfeld; April/May 2014]. None of these hypotheses, however, has yet to garner convincing research support. As we learn more about this widely misunderstood intervention, we may be able to refine our delivery methods and reduce ECT's negative effects. Even in its current form, however, the treatment is a far cry from the barbaric punishment portrayed in the media. Hence, it is often worth considering as an option for unremitting psychological distress after all else has failed. M

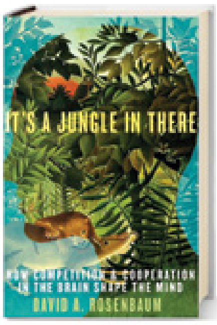
FURTHER READING

- **Shock: The Healing Power of Electroconvulsive Therapy.** Kitty Dukakis and Larry Tye. Avery Publishing Group, 2006.
- **Hollywood and ECT.** Andrew McDonald and Garry Walter in *International Review of Psychiatry,* Vol. 21, No. 3; pages 200–206; June 2009.

YOU ARE DARWINIAN

It's a Jungle in There: How Competition and Cooperation in the Brain Shape the Mind

by David A. Rosenbaum.
Oxford University Press, 2014 ($29.95)



Natural selection—the causal mechanism that Charles Darwin showed was responsible for the origin of new species—is difficult for many people to understand. It is not the simple linear kind of causation we see when the swing of a golf club sets a ball in motion. Linear causation is usually quick and obvious; selection by consequences takes time to work and is sometimes difficult to detect. You know it has occurred when (a) a number of interconnected events compete for resources in the environment, (b) some of those events are selected as being superior and (c) subsequent occurrences of those kinds of events now look more like the ones that were selected. The selection process changes probabilities; it strengthens the fit and weakens the unfit.

In 1978 Nobel laureate Gerald Edelman theorized that Darwinian competition among neural circuits might underlie the experience of consciousness itself. Now Rosenbaum, a psychology professor at Pennsylvania State University, asserts that the entire cognitive world operates along Darwinian lines—that competition among the neural circuits underlying motor behavior, thinking, memory and perception accounts for everything we think, say and do.

This is a radical idea, especially in one aspect. Just as Darwin's theory eliminated the need for a "designer," Rosenbaum's "jungle theory" eliminates the need for an "executive." There is, he insists—and contrary to what common sense and experience seem to tell you—no central, supervising *self* inside you that is composing sentences, making decisions and shifting attention. Instead a population of behavioral and perceptual tendencies is in constant competition with one another, strengthened or weakened by cues and consequences in the environment. How they *sum* at any moment in time determines what you do. You are, in effect, a "plurality."

The alternative, Rosenbaum says, is untenable—namely that there is an entity inside you who directs what you do but whose behavior we must in turn explain.

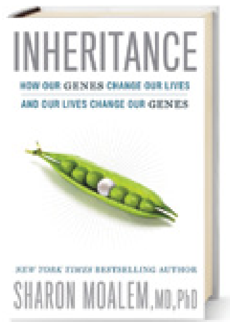
Unfortunately, this exciting idea gets lost at times when Rosenbaum sinks into the esoterica of technical experiments from the field of cognitive psychology. Of greater concern, he admits that his theory is "more a sketch than a complete theory." How, physically, does the competition and selection process work? Rosenbaum can't say.

These problems aside, *It's a Jungle in There* deserves to be selected. It presents a bold idea that puts human cognition squarely onto the shoulders of giants in the natural sciences, Darwin among them. *—Robert Epstein*

GENE PERSUASION

Inheritance: How Our Genes Change Our Lives—and Our Lives Change Our Genes

by Sharon Moalem. Grand Central Publishing, 2014 ($28)



Imagine you are at a dinner party with your spouse, but you can't keep your eyes off the host, enthralled as you are by the curve of her neck. For many, this might warrant a heated spousal talking-to. And so it does for Moalem, a specialist in rare genetic disorders, though not for the reasons you might think.

For Moalem, certain features—the cleft of a chin, the space between eyes, even extra eyelashes—may signal rare developmental and genetic diseases. In this case, to Moalem, the web of skin between neck and shoulder suggests Noonan syndrome, a disorder associated with heart defects and other problems. (He later discovered his suspicion was correct.)

As Moalem details in his new book *Inheritance,* the study of rare genetic diseases serves an important purpose. These disorders, which usually stem from mutations in a single gene, give scientists a better idea of what that gene does. These clues are important not just for treating carriers of the mutations but also for understanding other diseases. For instance, a mutation in a receptor for growth hormone causes an extreme shortness called Laron syndrome. Those with the syndrome are unusually resistant to cancer. This inverse association, which suggests a link between growth hormones and malignancy, points the way toward new potential cancer treatments.

Genes are often turned on and off, up or down, not by mutations, it turns out, but by environmental factors. Which brings us to the central thrust of Moalem's book: genes may be immutable, but how they are translated into flesh and blood absolutely is not.

Consider the honeybee. The only difference between a hive's queen and the sterile worker, both of which have the same genes, is diet. If a bee larva gorges endlessly on royal jelly, it matures into a queen. If it consumes just a few days' worth of jelly, it becomes a worker.

Mammals are not so different. Make a mouse pup anxious daily by removing it from its mother, and it becomes prone to a rodent form of depression in adulthood. Here is the kicker: pups born to this tormented animal inherit the same depressive tendency, even without experiencing the original torment. The transmission occurs not by genetic mutation but by epigenetic modification—the silencing or unsilencing of genes. This is how "our lives change our genes," which is both an empowering and, if our lives are not so great, frightening concept.

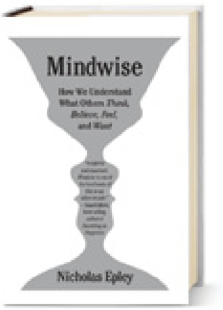
One of the more surprising takeaways is that the long-promised era of personalized medicine—where doctors tailor treatments to your particular genome—is arriving piecemeal. Currently available tests can detect important genetic variants. One variant prevents carriers from breaking down the sugar fructose, which can become hazardous if these individuals consume too much fruit. Despite their usefulness, such tests are not necessarily routinely conducted.

Inheritance is a wide-ranging and breezily written survey of an immensely important field—the science of how we may "tweak" our fixed genetic heritage to produce health and well-being. The narrative moves quickly, and what the book lacks in depth it more than makes up for with breadth, providing a solid foundation for readers. It is especially thrilling for a geneticist, of all people, to emphasize "it's not only what our genes give us that's important, but also what we give to our genes." *—Moises Velasquez-Manoff*

OUR FLAWED SIXTH SENSE

Mindwise: How We Understand What Others Think, Believe, Feel, and Want

by Nicholas Epley. Knopf, 2014 ($26.95)



"Speech was given to man so that he might hide his thoughts," wrote French novelist Stendhal. Research on how accurate we are in assessing how other people perceive us confirms his cynical assertion; the impression people give us generally corresponds poorly to their real views.

In *Mindwise,* Epley, a social psychologist at the University of Chicago Booth School of Business, expertly reviews a wide range of work of this kind to help us understand our "*real* sixth sense": our ability to make accurate inferences about what other people are thinking. Even by age two, humans are far better at making such inferences than the most intelligent animals are—but we *never* get very good at it.

This is important because accurate mind reading is fundamental to successful social interactions. If you believe everyone at the office party is thinking how silly you look in your new Rudolph-the-reindeer tie—even though no one is in fact paying the least attention—you might hide in a corner. If former French president Nicolas Sarkozy thinks Israeli prime minister Benjamin Netanyahu is not making good eye contact, he might infer—as indeed he did in 2011—that Netanyahu is "a liar." In other words, the future of your job and relationships and even the future of humankind may depend on the accuracy of that sixth sense.

Unfortunately, the research on this topic is discouraging. Epley even admits that the main goal of the book is "to reduce the illusion of insight you have into the minds of others"—in other words, to burst your bubble of self-deception. There may be advantages to acknowledging one's mind-reading deficits: you will be less likely to rush to judgment, he says, and more likely to give others the benefit of the doubt.

Toward the end, when it looks like Epley is finally going to show us how to overcome our deficits, we are let down. If you really want to know someone's mind, he says, forget the two most commonly recommended methods: evaluating gestures and facial expressions and trying to imagine the other person's perspective. Current research shows that lies are difficult to detect, even for highly trained TSA personnel, and that perspective taking actually makes one *less* accurate in knowing a person's mind. Instead, he says, just *ask* what someone is thinking. In other words, forget mind reading; we need "to rely on our ears more than on our inferences." That's all he wrote.

In short, *Mindwise* is a comprehensive and well-written overview mainly of things most people would rather not know, much like a textbook on heart disease, but without the cures.

—*Robert Epstein*

ISTOCKPHOTO

ROUNDUP

CREATING CONVICTIONS

Three books explore why we believe and how to become a skeptic

Why do some adults believe in creationism despite incredible evidence against it? In **Believing: The Neuroscience of Fantasies, Fears, and Convictions** (Prometheus Books, 2013), psychiatry professor Michael McGuire reports that our brain is designed to create beliefs, even misinformed ones, about the world in which we live. These attitudes often form outside our conscious control and profoundly bias how we think and behave. By understanding the pitfalls of this system, McGuire hopes we can learn to question, even change, our ideas.

Unearthing our inner skeptic, however, may be difficult, especially in the face of increasingly sophisticated and persuasive neuromarketing strategies. In **The Brain Sell: When Science Meets Shopping** (Nicholas Brealey, 2014), psychologist and neuromarketing expert David Lewis gives us the inside scoop on how advertisers manipulate our emotions, using smells, colors, catchy slogans, unconscious biases and even subliminal messaging, to get us to buy things. For instance, Starbucks tries to play on our emotions, not necessarily a love of quality coffee, by creating a "feeling of warmth and community," writes CEO Howard Schultz. The best way to combat these strategies, Lewis says, is simply to be aware of them.

But being aware is not enough. In **Think: Why You Should Question Everything** (Prometheus Books, 2013), journalist Guy Harrison says we must also become skeptics. Harrison discusses how everyone carries personal biases, engages in flawed thinking and has imperfect memory recall, which is why employing critical-thinking strategies is crucial. Learning to question our perceptions and do our own research, Harrison says, is not only good for our brain. It also helps us resist manipulation and make more reasoned judgments.

—*Victoria Stern*

Have a question?
Send it to editors@SciAmMind.com

Q

I have Asperger's syndrome, and my mum explained to me that my "brain works differently from everybody else's." I'm curious as to how this is so.

—**Emer McHugh,** Ireland

Simon Baron-Cohen, professor of developmental psychopathology at the University of Cambridge and director of the Autism Research Center, replies:

Your mother is correct that the scientific evidence points to the brain of people with autism and Asperger's syndrome as being different but not necessarily "disordered." Studies have shown that the brain in autism develops differently, in terms of both structure and function, compared with more typical patterns of development, and that certain parts of the brain are larger or smaller in people who have autism compared with those who have a more typical brain.

One structural difference resides in the brain's corpus callosum, which connects the right and left hemispheres. Most studies show that the corpus callosum is smaller in certain sections in people with autism, which can limit connectivity among brain regions and help explain why people with autism have difficulty integrating complex ideas.

An example of a functional difference is in the activity of the ventromedial prefrontal cortex, which is typically active in tasks involving theory of mind—the ability to imagine other people's thoughts and feelings—but is underactive when people with autism perform such tasks.

The brain of those with autism also shows advantages. When some people with this condition are asked to complete detail-oriented tasks, such as finding a target shape in a design, they are quicker and more accurate. Additionally, those with autism generally exhibit less activity in the posterior parietal cortex, involved in visual and spatial perception, which suggests that their brain is performing the task more efficiently.

Autism is just one manifestation of atypical neurodevelopment. There are hundreds of ways for the brain to wire itself, and each confers a different profile of strengths and weaknesses. This idea of neurodiversity most likely will be part of a changing way of thinking about autism.

Here is one illustration of the concept of neurodiversity: I am naturally left-handed, but as a four-year-old child in the 1960s I was forced by my primary school to write with my right hand because left-handedness was regarded as abnormal. Although this policy may have had no adverse consequences, we now accept that the 13 percent of boys and 8 percent of girls who are naturally left-handed are simply different, and we do not need to coerce people to all develop in the same way.

Some may try to place a value judgment on certain developmental profiles being "better" than others, but better is relative to the environment in which you find yourself. As one person with autism put it: "We are like freshwater fish in saltwater. Put us in freshwater, and we flourish. Put us in saltwater, and we struggle."

If you are a left-handed child in a world that insists you should be right-handed, then left-handedness becomes a disability. Remove the requirement to be right-handed, and "magically" the disability vanishes. Extend this to those with autism, in a world that expects every child to be sociable and communicate through face-to-face chatting and "small talk," and many people on the autism spectrum will be considered disabled. Remove this expectation, and a significant proportion of the autism community can function extremely well.

This is why I prefer using the term "autism spectrum condition" (ASC), instead of the American Psychiatric Association's diagnostic term "autism spectrum disorder" (ASD). Although my term changes only one word, it represents an important shift. ASC carries the same message that people on the autism spectrum have a disability, with a biomedical basis, but it avoids the implication that it is the result of the brain being somehow damaged.

But we need to be clear: neurodiversity does not equate to relativism. Relativism says that all neurological profiles are equal, but we know that some of them mean the individual can cope well only in a specific environment, and such people will be at a disadvantage compared with those who can cope with a wider range of environments.

Autism, however, is perhaps more like visual or hearing impairment than left-handedness, in that some functions such as theory of mind are compromised. Given that such abilities make social relationships much easier, this deficit helps to explain why autism does lead to disability.

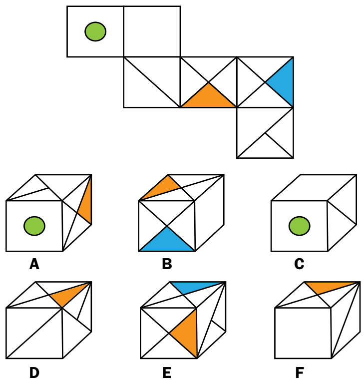
Let us assume that most of those with autism would prefer to have a typical theory of mind because it would make life easier for them. Yet when treatments come along, we need to ensure that they target only the features of autism that are disabling, leaving the positive facets—the excellent attention to detail, the ability to pursue a topic in enormous depth, the ability to quickly identify repeating patterns in a system—free to blossom.

Whether treatments exist or not, we should aspire to make the world more autism-friendly. Given that for every one person with autism there will be 99 without it, the risk will always exist that people with autism will feel they are on the margins. Being aware of their difficulties and adapting our behavior to be understanding and inclusive is half of the solution. M

JAMIE CARROLL *iStockphoto*

1 CUBISM

Which of the six boxes below cannot be made from this unfolded box? (There may be more than one.)



2 MULTIGRAM

Make as many common English words as you can from the letters AEKL, using all the letters each time.

3 PATTERN RECOGNITION

What two-digit number would most logically come next in the following sequence?

101 92 837 46 556 47 382

4 MENTAL GYMNASTICS

What number is two thirds of one half of one fourth of 288?

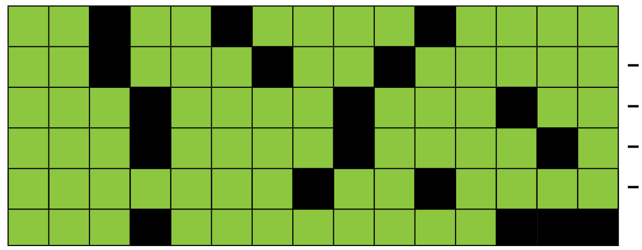
5 MISSING LINK

Each group of letters below is a jumbled word that has one letter missing. The same letter is missing in all six words. Find the letter and unscramble the words.

ENCU RUEC CATU
RCHA IOAR ANVI

6 WORDS OF WISDOM

The boxes below hold a quotation. The letters of the quotation have been put in alphabetical order by columns in the "drop-in" boxes below the table. Word divisions are indicated by black squares, and a dash at the end of the line indicates a broken word. What is the quotation?



E	E	G	E	I	E	D	A	B	I	A	E	A	L	B
H	N	H	I	R	H	D	E	N	T	H	H	E	O	D
I	N	R	W	S	I	E	E	R	T	H	N	G	R	L
I	O	T		S	N	T	N	U	Y	S	R	T	U	M
O	T			U	N	V	R		Y		S			T
T	T			W							T			

7 HIDE-AND-SEEK

The name of a country is hidden in each of the sentences below. Find the countries.

The doorbell sign said, "Don't touch. In a real emergency, pull the cord."

They got married secretly, but no one is wed entirely alone, so there were witnesses.

We needed to visit a health resort, so we went to a spa in another town.

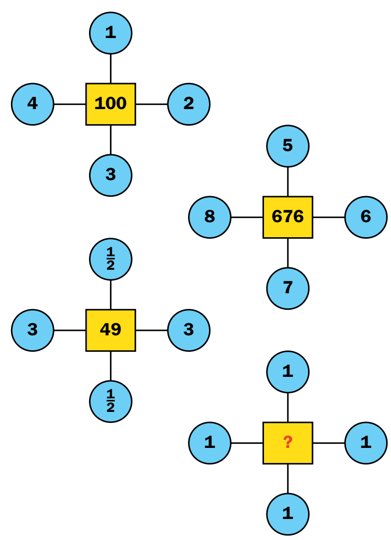
8 MANAGRAM

Each of these men's names except one can be anagrammed into a common English noun. Which name cannot be made into another word?

CORNELIUS DANIEL CAMERON
THOMAS BOSWELL

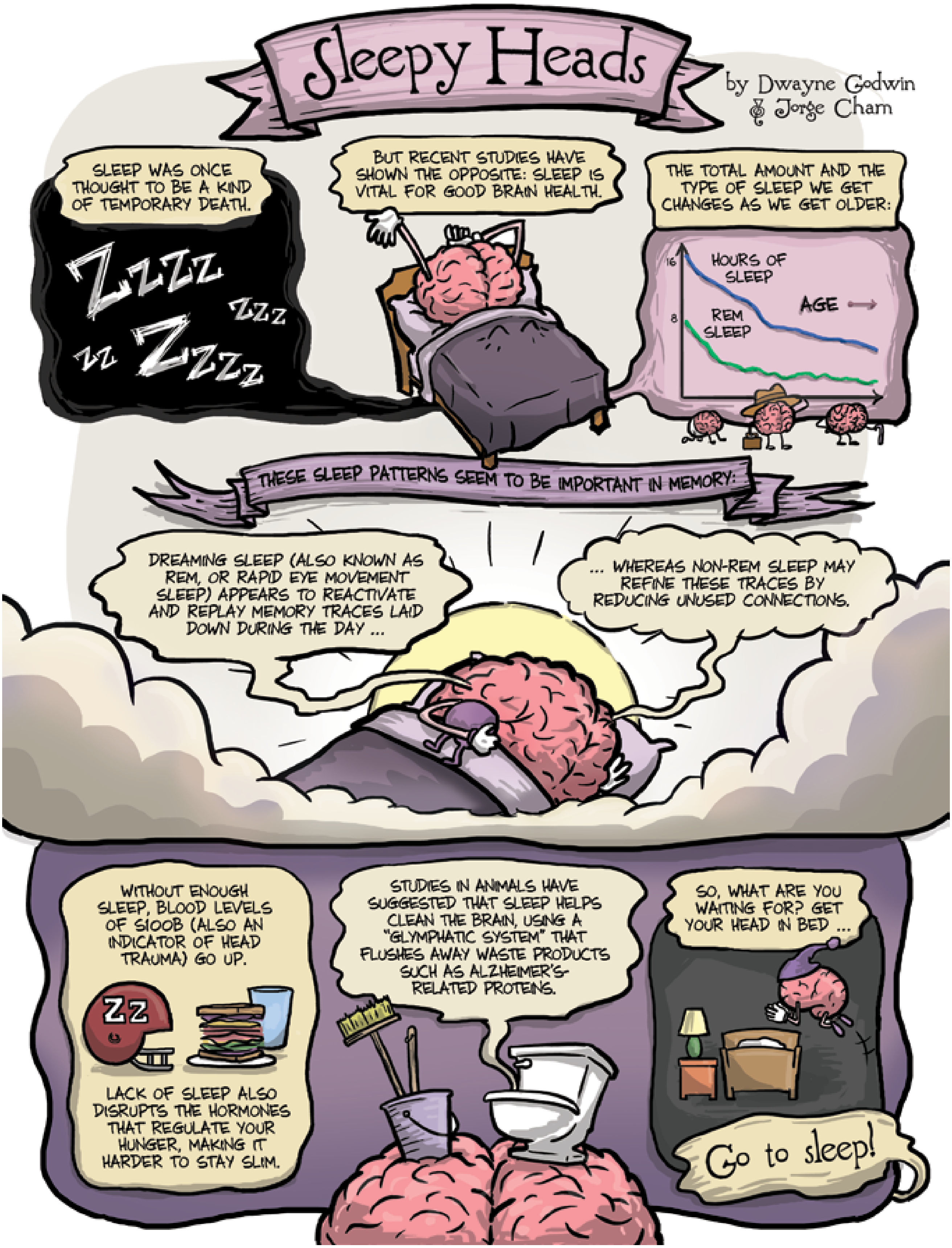
9 NUMBER SENSE

The numbers in each diagram below relate to one another following the same rules. Fill in the missing number.



Answers

1. A and D.
2. KALE, LAKE, LEAK.
3. 91 (look at every other digit).
4. 24.
5. The missing letter is D: DUNCE, CRUDE, DUCAT, CHARD, RADIO OR DORIA, DIVAN OR VIAND.
6. IT IS VERY HARD TO WIN AN ARGUMENT WHEN THE OTHER SIDE ISN'T BOTHERED BY TELLING UNTRUTHS.
7. CHINA, SWEDEN, SPAIN.
8. THOMAS.
9. 16.



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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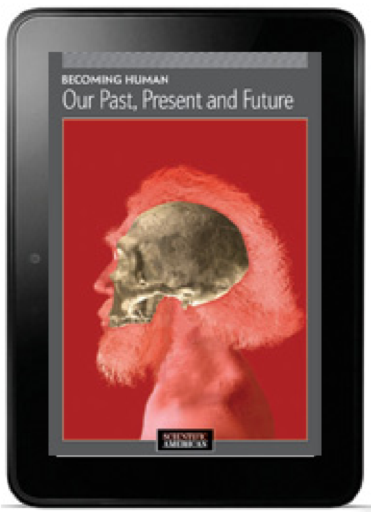
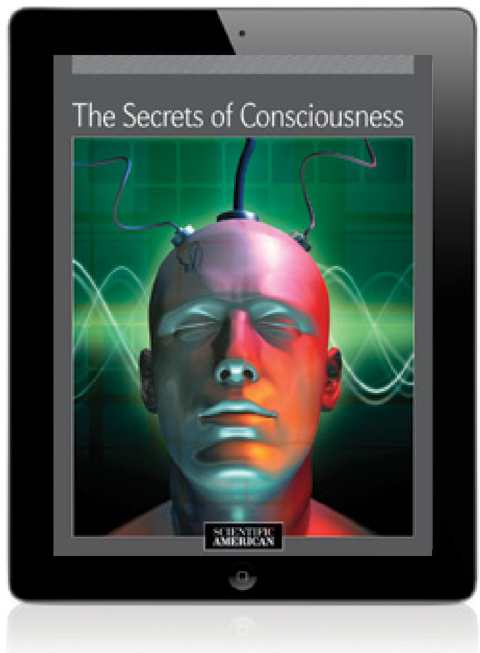
EBooks that raise your tablet IQ

Science to enrich your life in a format to fit your lifestyle
From the Editors of Scientific American



We humans are a strange bunch. We have self-awareness and yet often act on impulses that remain hidden. We were forged in adversity but live in a world of plenty. How did we get here? What is to become of us? To these age-old questions, science has in recent years brought powerful tools and reams of data.



Consciousness is an enigmatic beast. It's more than mere awareness—it's how we experience the world, how our subjective experience relates to the objective universe around us. Once the province of philosophy, religion or perhaps fantasy, neuroscientists have added a scientific voice to this discussion, using available medical technology to explore just what separates so-called "mind" from brain.

Advances in technology often concur with times of war—the nuclear bomb is an iconic example. The need to develop a weapon before the Nazis changed the rules of warfare forever. Today each advance from drones to computer systems to biological weapons demands a re-thinking of where the vulnerabilities lie and how severe any collateral damage would be.

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