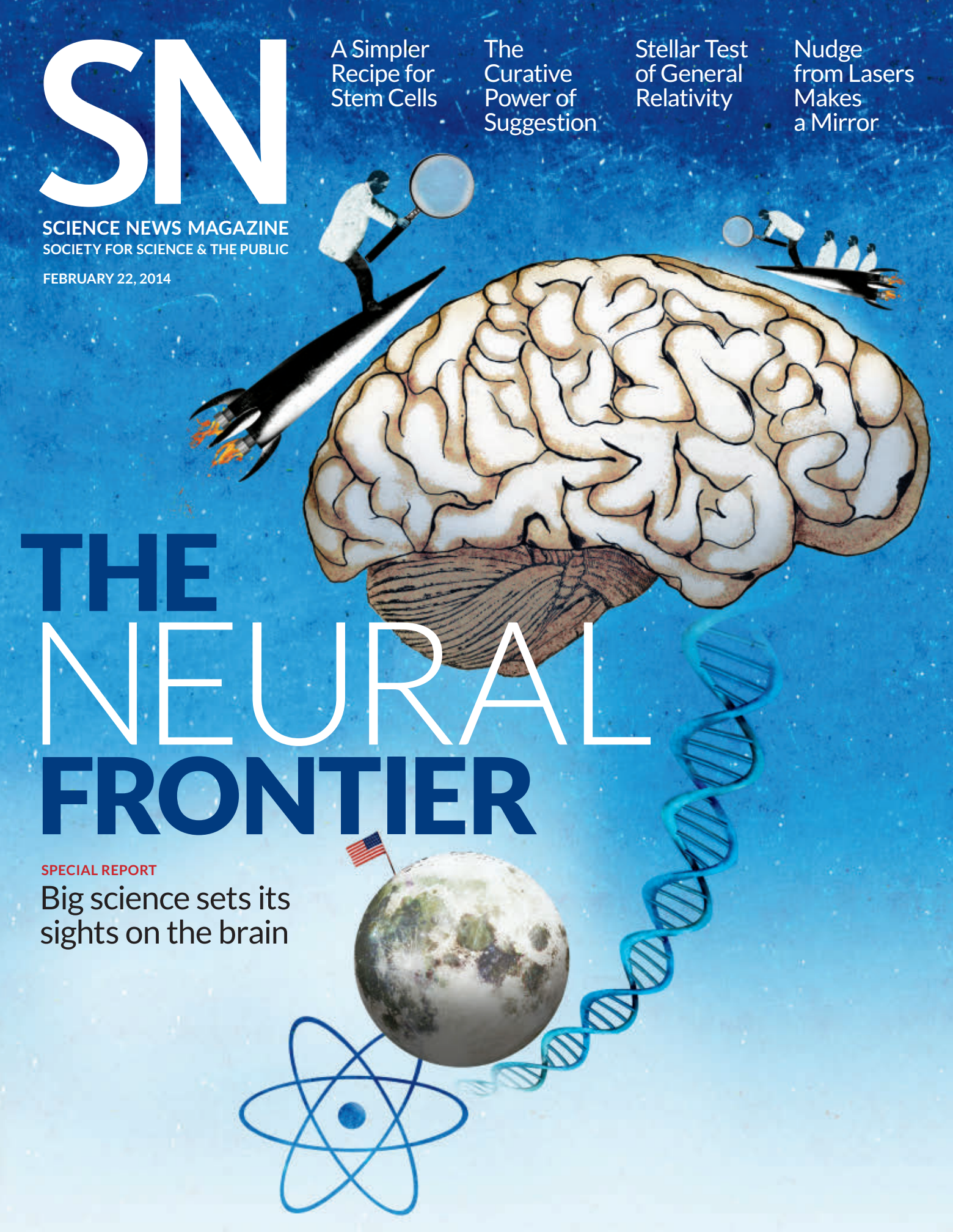
SN
SCIENCE NEWS MAGAZINE
SOCIETY FOR SCIENCE & THE PUBLIC
FEBRUARY 22, 2014

A Simpler Recipe for Stem Cells

The Curative Power of Suggestion

Stellar Test of General Relativity

Nudge from Lasers Makes a Mirror



THE NEURAL FRONTIER

SPECIAL REPORT

Big science sets its sights on the brain

Chemistry Casanova Reinvents the Emerald

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ScienceNews

Special Report

BIG NEUROSCIENCE

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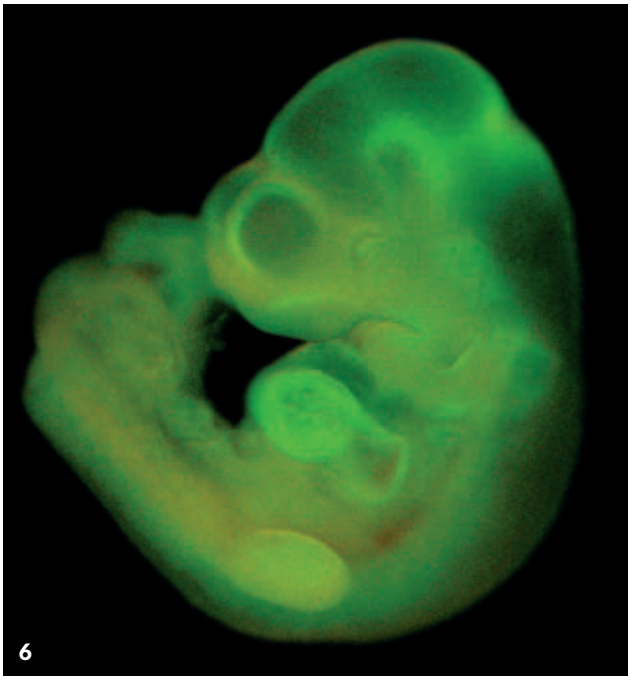
News



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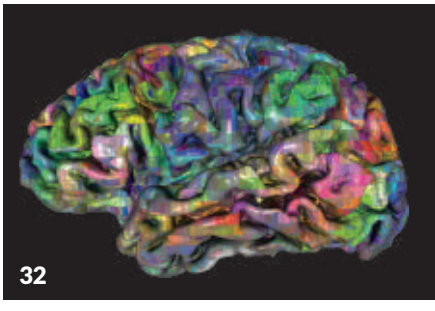

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Departments

COVER Like the Apollo Program and other major scientific efforts, the BRAIN Initiative has big goals that will be tough to reach. *Michael Morgenstern*

CLOCKWISE FROM TOP LEFT: COURTESY OF OPENWORM AND VIRTUAL WORM; ALEX HUTH, JAMES GAO AND JACK GALLANT/UC BERKELEY; H. OBOKATA

Big science for lean times

Efforts to make sense of the morass of cells and signals that populate the brain have come a long way in the last 50 years. Scientists have examined the signaling of single neurons in great detail, revealing much about the electrochemical mechanisms that carry messages from one cell to the next. Modern scanning technologies have enabled unprecedented if high-altitude views of the brain's inner workings, pinpointing functional units of the brain (see Page 32). But the greatest promises of brain research — a cellular description of thought and behavior and, even more importantly, strategies to battle disorders of the brain — have yet to be fulfilled.

Making good on those promises is the motivation behind the federal BRAIN Initiative, proposed by President Barack Obama last year (*SN: 5/4/13, p. 22*), now in the process of being further articulated by neuroscientists and the focus of a special report in this issue. One goal is to develop a view of the middle ground: how individual neurons hook up in circuits and coordinate their activity en masse to give rise to the regions lit up in a brain scan. Some progress on the daunting problem of mapping all of the brain's connections has already been made, as Tom Siegfried describes on Page 22. But the initiative espouses a broad array of additional goals, including the invention of new tools to study and manipulate thousands of neurons at once.

As Laura Sanders reports on Page 16, the initiative may well be one of the most ambitious big science projects ever proposed, à la the Manhattan Project, the Apollo Program and the Human Genome Project. But, so far at least, this is big science on a much smaller scale, with limited resources, no unified plan and no simple metric of success.

It sounds like *Mission Impossible*. But it's worth doing. Even if scientists don't reach the many lofty goals outlined so far, they still have the potential to make great progress. And the exercise of creating a road map for neuroscience in the 21st century will not be a wasted effort even if all of those milestones aren't reached until the 22nd century. The real value of the Human Genome Project, after all, wasn't the complete DNA contents of a person. It was the creation of tools to collect and analyze genetic information that have revolutionized views of the natural world.

— Eva Emerson, Editor in Chief

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Science News (ISSN 0036-8423) is published biweekly by Society for Science & the Public, 1719 N Street, NW, Washington, DC 20036.

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Subscribing memberships include 26 issues of *Science News* and are available for $50 for one year (international rate of $68 includes extra shipping charge). Single copies are $3.99 (plus $1.01 shipping and handling). Preferred periodicals postage paid at Washington, D.C., and an additional mailing office.

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SANDY SCHAEFFER

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Fairy Tales

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Excerpt from the February 22, 1964, issue of *Science News Letter*

50 YEARS AGO

Moon Like Blue Cheese?

The moon's surface is probably closer to green cheese than to solid rock. Blue cheese may be more accurate than green when an astronaut finally steps off into the rough, dark, opaque material left by micrometeorite bombardment. Dr. Thomas Gold, director of the center for radiophysics and space research, Cornell University, Ithaca, N.Y., said that the action of micrometeorites on the moon's surface cannot fail to produce at least a thin layer of finely pulverized material like dust.... Dense particle packing is possible so that a moon visitor would be able to make his way about in a weightless condition.

UPDATE: When Apollo 11 astronauts reached the moon, dust covered their spacesuits and equipment. Apollo missions left behind lunar dust detectors, but the data were not analyzed for more than 40 years. In November 2013, researchers reported in *Space Weather* that about a millimeter of lunar dust is added each 1,000 years, about 10 times faster than previously thought (*SN: 1/11/14, p. 6*).

Packrats will hoard just about anything, even cactus needles, to use in building their nests.

IT'S ALIVE

'Packrat' is the new term for 'really organized'

A real packrat doesn't store junk in its bedroom. Or its bathroom.

Its midden home may look like a heap of sticks, but inside, what a floor plan. What storage. The more eclectic hoarder species segregate pantry from lumber room from junk museum. The result is more orderly than the closets of some human packrats.

Some packrats like variety, while others specialize. *Neotoma stephensi* packrats hoard only juniper twigs, which make up 90 percent of their diet despite the plant's toxicity. Packrats and the rest of their *Neotoma* woodrat cousins have quirky digestive systems more common in big grazing animals than in small mammals, allowing them to digest tough and even toxic foods. "You can think of them as a miniature goat," says Michele Skopec of Weber State University in Ogden, Utah. "They eat all kinds of crazy stuff."

A packrat midden (shown under the hood of an abandoned car) is a single-rodent home that can shelter a long series of owners.

Neotoma albigula packrats, also called white-throated woodrats (above), collect a variety of crazy stuff too. They bring home abundant cowpats, rabbit pellets and other animals' dung, often leaving it just outside the midden. Inside middens Skopec has found an old underwear band, a silvery ring, shotgun shells, a coyote paw, Doritos bags and much more.

Unlike satin bowerbirds, which decorate mating sites with such treasures as pen caps and clothespins, packrat collectibles aren't on display. "They're solitary animals," Skopec says. "It's not as if they're bringing others in and saying, 'Look at how sweet my interior is.'" Some of their stockpile is building materials, bedding or food, but the rest remains a mystery.

Searching for patterns in collecting, she and her students gave 10 white-throated woodrats a choice of jingle bells. In the lab, packrats pretty much liked it all. Shiny was as good as matte. Blue, the color of juniper berries they eat, didn't appeal more than gold. Nor did jingly instead of silenced, or bells versus wads of paper and toothpicks. "They have this insatiable urge to cache," Skopec says.

What so far appears to make a difference is the scent of another woodrat. These solitary-living, ferocious collectors may be disinclined to steal each other's bling. — *Susan Milius*

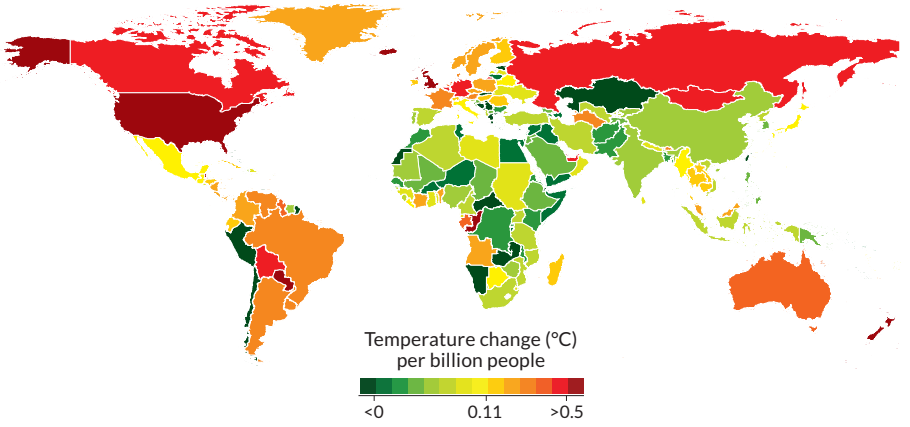
FROM TOP: GREGORY SMITH/FLICKR; COURTESY OF M. SKOPEC

SCIENCE STATS

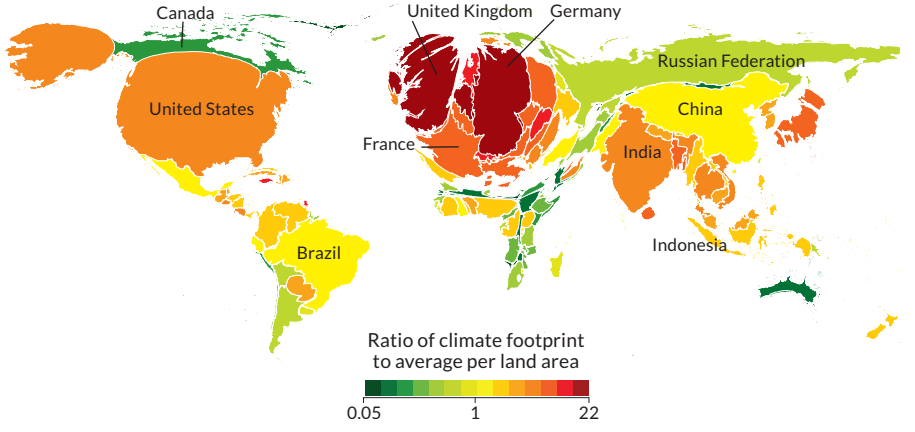
Biggest climate warmers

The United States, China, Russia, Brazil, India, Germany and the United Kingdom are responsible for more than 60 percent of the 0.74 degree Celsius rise in global average temperature observed from 1906 to 2005, a new report shows. Nations add to warming through fossil fuel use, land-use change and other effects. In a cartogram (bottom left), a nation's size expands if its warming contribution is large for its geographic area and contracts if emissions are low per unit area. SOURCE: H.D. MATTHEWS *ET AL/ENVIRON. RES. LETTERS* 2014

Contribution to warming, by population



Contribution to warming, by land area

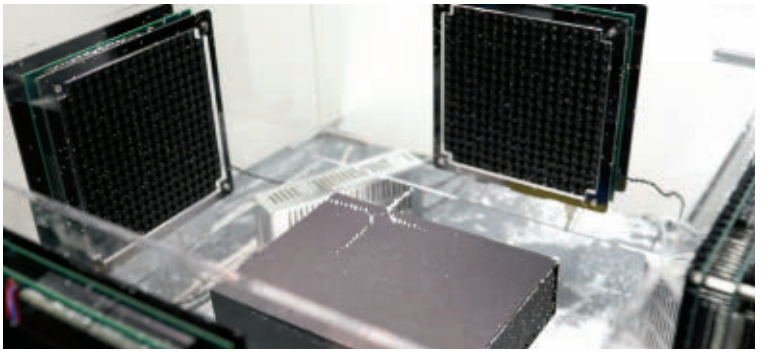


22 percent
U.S. contribution to total global temperature rise, 1906–2005

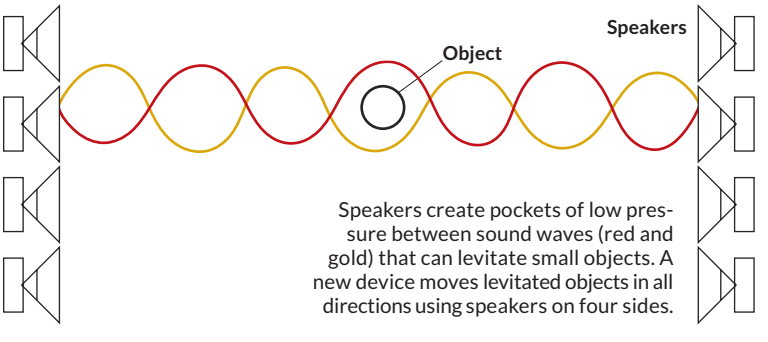
HOW BIZARRE

Controlled hover

Step into Jun Rekimoto's lab at the University of Tokyo and you might see a screw floating through the air. Don't worry, it's normal: Rekimoto's team has built a new device that uses sound to levitate objects and — for the first time — maneuver them in all directions. For decades physicists have levitated millimeter-sized objects by trapping them in pockets of low pressure between the crest of one sound wave and the trough of another. But moving those suspended objects has been difficult. Rekimoto's team set up four arrays of speakers pointed at the center of a half-meter-wide chamber. Once the researchers got an object hovering, they tweaked the intensity of waves in each array to move the object up and down, left and right, and back and forth. They describe manipulating beads, feathers and alcohol droplets December 14 at arXiv.org. Eventually the technique could remotely mix compounds to create pharmaceuticals without impurities. — *Andrew Grant*



How acoustic levitation works



Speakers create pockets of low pressure between sound waves (red and gold) that can levitate small objects. A new device moves levitated objects in all directions using speakers on four sides.

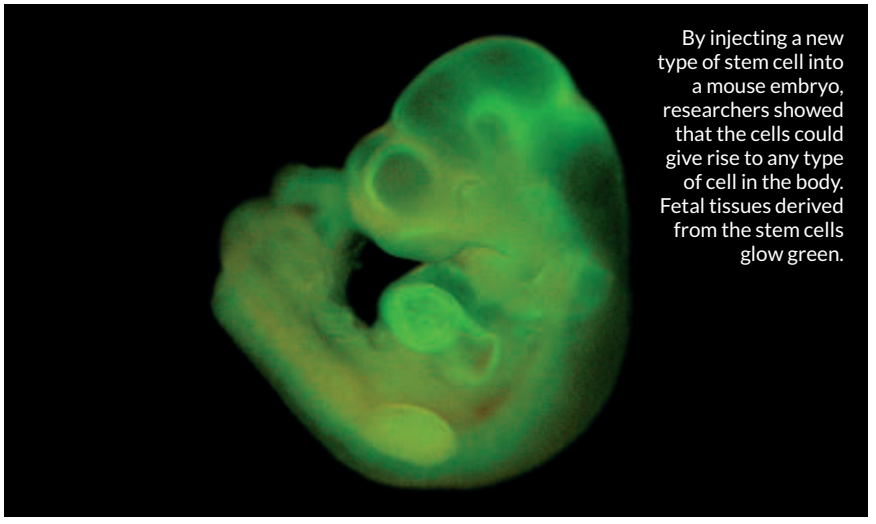
Watch a video of acoustic levitation at **bit.ly/SNsoundfloat**

TOP: MODIFIED BY S. EGTS; BOTTOM: YOICHI OCHIAI/UNIV. OF TOKYO, DIAGRAM MODIFIED BY S. EGTS

GENES & CELLS

A little acid can make a cell stemlike

Mouse cells enter primordial state capable of making any tissue



By injecting a new type of stem cell into a mouse embryo, researchers showed that the cells could give rise to any type of cell in the body. Fetal tissues derived from the stem cells glow green.

H. OBOKATA

BY TINA HESMAN SAEY

Creating stem cells may be as simple as dunking cells into a mild acid bath.

Doing so turned cells from newborn mice into ultraflexible stem cells that could grow into any type of body tissue, researchers report in the Jan. 30 *Nature*. Other stresses, such as squeezing cells through glass tubes, can also reprogram cells, Haruko Obokata of the RIKEN Center for Developmental Biology in Kobe, Japan, and Brigham and Women's Hospital in Boston and colleagues discovered.

If it works on human cells, the technique could provide replacement cells for diseased body parts, foster a better understanding of a person's disease risks and drug sensitivities and maybe serve as a fertility treatment.

The method has floored other researchers, who thought that creating stem cells required more complex operations: extracting cells from embryos, transferring the nucleus of an adult cell to an egg cell or using viruses or other means to introduce factors that coax an adult cell to behave like an embryonic stem cell.

"It's fascinating. It's perplexing. It's potentially profound, but leaves lots of reasons to scratch my head," says George Daley, a stem cell researcher at Boston Children's Hospital and Harvard Medical School. "It's begging to be replicated," he says, adding that his lab will attempt to do just that.

In the new study, about 7 to 9 percent of cells from newborn mice survived the acid treatment and took just a week to form primordial cells, dubbed STAP cells for stimulus-triggered acquisition of pluripotency. Pluripotent cells can develop into cells of any tissue. Both embryonic stem cells and reprogrammed cells known as induced pluripotent stem cells, or iPS cells, are pluripotent.

STAP cells may be even more flexible, Obokata says. When injected into mouse embryos, STAP cells not only incorporated into any body tissue but could also form parts of the placenta. That's a feat other pluripotent cells generally can't accomplish, and it may indicate that STAP cells are totipotent, or capable of forming a complete organism.

Obokata and her colleagues transformed skin, brain, muscle, fat, bone marrow, lung, liver and white blood cells from 1-week-old mice into STAP cells. The technique worked, but not as well, on cells from young adult mice that were 6 weeks old, she says. The researchers have begun testing the acid treatment on human cells.

Dieter Egli, a stem cell researcher at the New York Stem Cell Foundation, is skeptical. "If I were to describe this over a coffee break to one of my colleagues, they'd say, 'You must be kidding,'" he says. He knows of no mechanism that could explain how mild acid or squeezing changes a cell's fate so dramatically and consistently in one direction. Egli wonders why, for instance, blood cells became stem cells instead of transforming into muscle or any other type of cell.

Cells undergo stress in daily life, Egli points out. If simple acid or mechanical stress causes cells to revert to an early developmental state, he says, "it's hard to imagine how our bodies would maintain integrity over a lifetime."

But Qi-Long Ying, a stem cell biologist at the University of Southern California in Los Angeles, speculates that the body produces inhibitory factors that prevent stress from reprogramming cells. Without those inhibitions, lab-grown cells can regress to an immature state. Understanding how stress reverts mouse cells to the anything-goes state may teach researchers more about cancer, another condition in which cells have no particular identity.

Ethical barriers may pop up on the road to using STAP cells. Because STAP cells may be totipotent, UCLA stem cell researcher James Byrne worries that the new technology may raise old specters of human cloning. Acid-reprogrammed cells potentially could grow into a fetus, placenta and all. If that's true, the cells might treat infertility by creating an embryo from an adult's cells, Byrne says.

Still unclear is whether researchers will choose STAP cells over other types of stem cells, says Louise Laurent, a stem cell biologist at the University of California, San Diego. Regardless, she says, the work "will inspire people to explore less traditional ways of changing a cell's fate." ■

Watch a video of a mouse fetus grown partially from STAP cells at **bit.ly/SNstemcell**

Thinking hard weighs heavy on a person's brain

Balance measures tiny changes in force due to blood flow during mental tasks

BY LAURA SANDERS

When the mind is at work, the brain literally gets heavier.

That fact may be surprising, but it isn't new: In the 1880s, Italian scientist Angelo Mosso built an intricate full-body balance and reported that mental activity tips the scales. Now, a modern-day version of Mosso's "human circulation balance" backs him up. Compared with a brain at rest, a brain listening to music and watching a video is indeed heavier, David Field and Laura Inman of the University of Reading in England report January 9 in *Brain*.

> "We have been neglecting Mosso and his work for so many years."
>
> **STEFANO SANDRONE**

While teaching a course about brain-imaging techniques, Field grew curious whether Mosso's general approach would work. So he and some students decided to find out. "It was a bit of a mad idea, to be honest," Field says.

At the heart of both balances lies a simple seesaw lever. As weight shifts in a body, presumably from the movement of blood, the lever tilts the head or the feet downward, Mosso observed. Field and Inman's contraption doesn't actually tip. The researchers put a sensitive scale under the head end, which would register changes in force.

After lots of troubleshooting, which involved eliminating signals created by blood moving in response to bodily processes such as breathing and heartbeats, Field and Inman could test mental tasks. Fourteen participants were asked to lie still on the lever and listen to music or listen to music and simultaneously watch a video of colorful geometric shapes. The part of the brain that detects sound is relatively small, Field says, so the audio plus video test was used to activate a wider swath of the brain and increase the chances of a measurable blood shift.

Right after a two-second blip of either audio or audio and video, blood leaves the brain, as measured by a drop in force, Field and Inman found. This quick dip in blood volume, a phenomenon that's also seen in functional MRI, may represent the brain preparing for work by shunting waste-ridden blood out via the jugular vein. Seconds after that, a surge of new blood enters the brain, raising the force above its starting point.

These changes in force were very small — about 0.005 newtons — and most prominent in the people who both listened to music and watched a video, Field says. It's difficult to calculate how much blood rushes into the brain with each mental task. To determine that value, scientists would need to know the distance of the head from the lever's fulcrum, which could be easily measured, and exactly where the blood came from, which is nearly impossible to know.

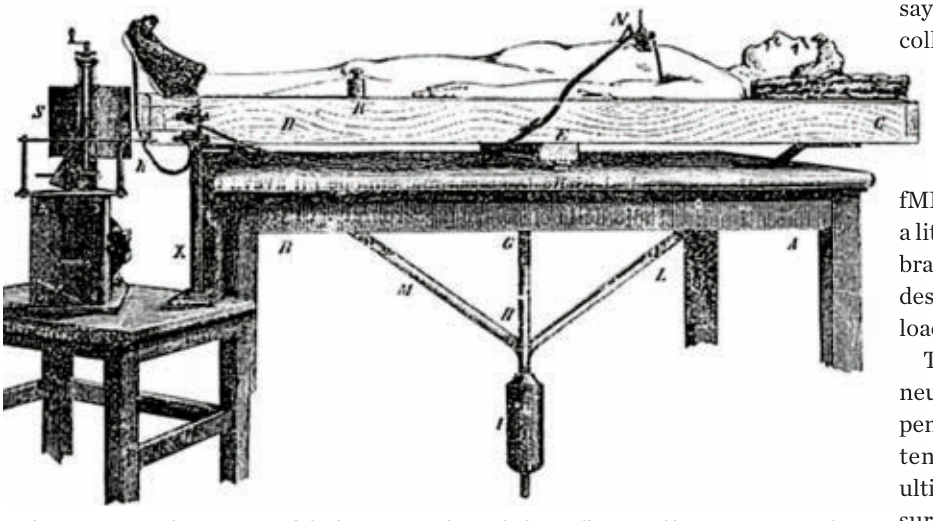
In his original experiments, Mosso found that tasks requiring more mental energy made the brain heavier. Reading a page from a math manual seemed to tip the balance more than reading a page from a newspaper. Strong emotions also tipped the scales: When a subject read a letter from an angry creditor, Mosso wrote, "the balance fell all at once."

Until recently, Mosso's scientific manuscripts had not been described in detail. But Stefano Sandrone of King's College London unearthed Mosso's papers in archives and published a description in *Brain* in 2013.

"We have been neglecting Mosso and his work for so many years. It's good that someone has begun to find interest in the papers that he wrote," Sandrone says of the new experiment. He and his colleagues are working on an exhibition of Mosso's original balance.

Many neuroscientists use functional MRI to detect changes in blood flow in the brain. Usually, fMRI spots regional differences, as when a little blood moves from one part of the brain to another. In contrast, the balance describes overall changes in brain workload, Field says.

The balance won't replace modern neuroimaging as a way to see what happens inside the brain. But Sandrone contends that with refinements, it might ultimately prove useful. "The more measures we have, the more we can approximate the complexity of the brain." ■



S. SANDRONE ET AL/BRAIN 2013

In the 1880s, Angelo Mosso used the human circulation balance illustrated here to measure the movement of blood to the brain during taxing mental tasks such as reading a math manual.

MATTER & ENERGY

Laser constructs mirror by pushing particles together

Technique may lead to giant, lightweight space telescopes

BY ANDREW GRANT

A focused beam of green light has transformed 150 plastic beads into a functional mirror. The feat is the first step toward an ambitious goal: deploying lasers in space to assemble a cloud of dustlike particles into a giant telescope mirror.

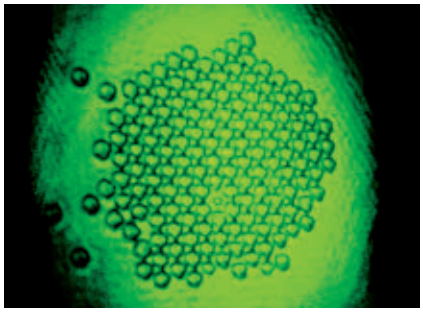
"I think it's really cool," says Michael Burns, a Harvard physicist. "It demonstrates something that had only been discussed before."

Most of the fundamental physics behind the idea of building space mirrors with lasers is solid, Burns says. Light provides a subtle push when it bounces off matter. It can also trap particles illuminated within a laser beam, which allows scientists to isolate individual cells and even atoms. Finally, light scattering off a particle can serve as a bonding force, enabling multiple particles to self-assemble into organized structures.

Exploiting these properties of light, astronomer Antoine Labeyrie proposed in 1979 that a pair of continuously firing lasers in space could steer billions of particles into a tightly bound parabola and hold them in place, creating an enormous, lightweight telescope mirror.

Since 2005, Tomasz Grzegorczyk of BAE Systems in Burlington, Mass., and colleagues have been analyzing the physics of the laser-and-particle interactions that would form this seemingly magical mirror. To build a rudimentary mirror, they placed a few hundred micrometer-sized plastic beads into a water-filled glass tank and shined a laser beam into the tank from below.

The laser pushed about 150 beads to the top of the tank against the glass and forced them together into a crystalline, reflective structure. To test their creation's reflectivity, the researchers projected an image of the numeral eight from a plastic ruler onto the mirror and used a camera to capture the reflected image. Despite the mirror's relatively rough surface, it delivered a fuzzy but recognizable reflection, the team reports January 13 in *Physical Review Letters*.



When illuminated with green laser light, about 150 plastic beads arranged themselves into a 40-micrometer-wide mirror.

T.M. GRZEGORCZYK *ET AL/PHYS. REV. LETT.* 2014

But NASA won't be commissioning a laser-assembled space telescope any time soon. Grzegorczyk's mirror is only about 40 micrometers across, and it relies on the surrounding water to absorb some of the laser's heat. There are also enormous technological hurdles, including the need for two powerful lasers that could run continuously for years in space to hold the mirror together. "With current technology, this is still closer to science fiction," Burns says.

Yet the potential performance of such a mirror in space is so extraordinary that Grzegorczyk says he can't quit. In theory, a pair of lasers could construct and maintain a 35-meter mirror, larger than any existing telescope mirror in space or on Earth. It would have the same mass as a hamburger patty. For comparison, the 6.5-meter mirror on NASA's James Webb Space Telescope, which is due to launch in 2018, has a mass of nearly 700 kilograms.

Because larger mirrors collect more light, a laser-constructed mirror connected to a camera potentially could image planets orbiting distant stars as well as galaxies at the edge of the visible universe. Plus, the mirror could heal itself: If space junk shattered a section, the lasers would nudge displaced particles back into position. ■

ATOM & COSMOS

Star trio promises new test of gravity

Analysis of unusual system could dethrone general relativity

BY GABRIEL POPKIN

A threesome of stars locked in tight, circular orbits could help astronomers test the leading theory of gravity to unprecedented precision. The discovery of the celestial trio is reported in the Jan. 23 *Nature*.

"We should be grateful to the universe for making such things," says Paulo Freire, an astrophysicist at the Max Planck Institute for Radio Astronomy in Bonn, Germany, who applauds the finding. "Part of me wishes I were involved."

Our galaxy is full of stellar couples and trios. But the formations and motions of the stars in PSR J0337+1715 make the system unique among those found by astronomers. The triad consists of an extremely dense, fast-rotating stellar corpse called a pulsar and two less massive dying stars known as white dwarfs. Pulsars form when white dwarfs at least 1.4 times larger than the sun blow up in supernovas; these explosions usually knock nearby stars out of their orbits. In PSR J0337+1715, however, the pulsar and one of the dwarfs circle each other in a 1.6-day orbit. The other dwarf orbits the inner stars at a larger distance, though still closer than the sun is to Earth.

Scott Ransom, an astronomer at the National Radio Astronomy Observatory in Charlottesville, Va., who discovered PSR J0337+1715 in telescope data, says he and his colleagues don't know how the stars could have come together in this way. But the researchers are excited

Zebrafish owe their stripes to the coordinated movement of at least two types of pigment-producing cells.

GENES & CELLS

How the zebrafish got its stripes

Yellow and black pigment cells chase each other into patterns

BY TINA HESMAN SAEY

Scientists have long puzzled over how animals' stripes, spots and other color patterns arise. One of the most popular theories was proposed in 1952 by mathematician Alan Turing, who showed that two chemicals spreading across a surface could spontaneously react to create patterns. By varying how chemicals diffuse and react under different conditions, Turing could reproduce many patterns seen in nature (*SN: 7/17/10, p. 28*).

Researchers have tried to find diffusing chemical signals in animals that might guide pattern formation. But research published January 21 in the *Proceedings of the National Academy of Sciences* suggests instead that interactions between yellow pigmented cells and black ones help create the stripes that give zebra fish (*Danio rerio*) their name.

"The long quest for the suggested long-range diffusible signals has not been as fruitful as originally expected," says Enrique Salas Vidal of the National Autonomous University of Mexico in Cuernavaca. Instead of diffusing chemicals, work by Hiroaki Yamanaka and Shigeru Kondo of Osaka University in Japan suggests, up-close communication between cells causes patterns to form during development.

Yamanaka and Kondo extracted pigment cells from zebrafish fins and watched the cells interact under a microscope. Yellow pigment cells called xanthophores reach out toward black pigment cells called melanophores. The black cells recoil and move away. Then the yellow cells extend projections called pseudopodia and give chase. The cells usually dance in a counterclockwise spiral around each other.

Mutations in some genes create either wide, fuzzy stripes in "jaguar" mutant fish or spots in "leopard" mutant fish. The researchers found that in fish with jaguar mutations, black melanophores circle yellow pigment cells but don't move away from them. In leopard mutants, the yellow xanthophores reach out toward the black cells but don't chase them. The black cells also don't run away. Those observations provide evidence that cell movement is important for pattern development in fish fins.

That doesn't mean Turing was wrong, Kondo says. "If we assume that the cell projection mimics the diffusion, the mathematical concept of the mechanism we found is very similar to the Turing model."

The team made a few assumptions that need testing, says Christiane Nüsslein-Volhard of the Max Planck Institute for Developmental Biology in Tübingen, Germany. For instance, the researchers say that the "run-and-chase" behavior of black and yellow cells accounts for stripes on zebrafish bodies as well as their fins, but she has evidence that iridescent cells called iridophores are also important for body stripes. The new study did not examine those cells. ■

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because the system's arrangement will allow them to probe gravity. As the pulsar spins 366 times per second, its magnetic field sweeps through space like a lighthouse beam. By measuring minute variations in the beam's timing, Ransom and his colleagues can precisely track the motions of all three stars in the system.

The team wants to see whether the stars are pulled toward each other as general relativity, the leading theory of gravity, predicts they should be. When a hyperdense object like a pulsar forms, part of its mass converts to energy that binds the object. General relativity's strong equivalence principle states that gravity should have the same effect on this binding energy as it would on an equivalent amount of mass. That means the pulsar and the inner white dwarf in PSR J0337+1715 would fall toward the outer white dwarf at the same rate. In nearly all competing theories of gravity, binding energy interacts with gravity differently than with mass, which would cause the pulsar and inner white dwarf to fall at slightly different rates.

Physicists think general relativity must eventually yield to a theory compatible with quantum mechanics, which describes nature at its smallest scales. All such theories that have been proposed would not contain the strong equivalence principle, Ransom says. Although his team should be able to measure gravity 100 times more precisely than ever before, Ransom hesitates to bet his measurement will be the one to overthrow general relativity, introduced by Albert Einstein in 1916. "Everything that we've ever looked at has shown that it works beautifully," he says.

Ransom's group has an opportunity to do a beautiful test, University of Florida physicist Clifford Will says. "If they could pull it off in the next year or two, it would be a great 100th birthday present for Einstein's theory." ■

THIERRY MARYSAEL/FLICKR

ATOM & COSMOS

Aging Mars rover finds signs of water

Rocks reveal ancient aquatic environment hospitable to life

BY MEGHAN ROSEN

Ancient Mars may have been a friendlier place for life than scientists once suspected. The veteran Mars rover Opportunity has dug up evidence that groundwater flowed near a giant crater called Endeavour about 4 billion years ago.

And like the ancient lake that rookie rover Curiosity recently explored at Gale Crater (*SN Online: 3/12/13*), the water at Endeavour was just right for microbial life: not too acidic or salty for cells to thrive, researchers report in the Jan. 24 *Science*.

"At two landing sites on completely different sides of the planet, we now see evidence for these very benign, water-rich environments," says Caltech planetary geologist Bethany Ehlmann, who is part of the Curiosity team. "That says a lot about how prevalent life could have been."

Opportunity began searching for signs of microbe-friendly water a decade ago, when it landed on Mars with its twin rover, Spirit. Before the end of its planned three-month mission, Opportunity found evidence that salty, acidic water could have once pooled at Meridiani Planum, a smooth, flat plain (*SN: 3/6/04, p. 147*).

Years later, the Mars Reconnaissance Orbiter picked up telltale signatures of iron-rich clay minerals — which form in the presence of chemically mild water — in Endeavour Crater, more than 20 kilometers from the site where Opportunity had been exploring. Since the rover had been trucking along years longer than expected, scientists sent Opportunity in for a closer look.

In 2012, to direct the rover to the right spot, planetary geologist Raymond Arvidson of Washington University in St. Louis and colleagues sharpened images from the orbiter and mapped the iron-rich clay minerals to an outcrop of rocks on Endeavour's rim. The minerals may have formed as slightly acidic water corroded basaltic rock, Arvidson says.

There, Opportunity found odd fractures cutting through the crater's rocks. The rover ground into the fractures with its rock abrasion tool, a kind of rotating nail file, and analyzed their ingredients.

The 10-year-old rover Opportunity casts a shadow over Mars' now-dry Endeavour Crater in a false-color mosaic image. The rover found evidence that billions of years ago the region hosted groundwater suitable for life.

"The deeper we went, the more it looked like aluminum clay, which requires a whole lot more water to form," Arvidson says.

The clay minerals hint that the ancient water's chemistry may have been favorable for life.

Other rocks that Opportunity sampled at Endeavour indicate that there's a long history of water in the region. Younger sandstone that overlies the ancient rocks bears evidence of a more acidic, less hospitable kind of water.

The new analysis comes almost exactly 10 years after Opportunity's touchdown on the Red Planet on January 24, 2004. "I can't believe this vehicle is still going," Arvidson says. "But it's a good American-made vehicle — it's like a '48 Chevy." ■

HUMANS & SOCIETY

Stone Age spearpoint found on Asian island

A 35,000-year-old piece of carved bone found on Timor, an island between Java, Indonesia, and Papua New Guinea, indicates that complex hunting weapons were manufactured much earlier than previously thought in Australasia.

A team led by archaeologist Sue O'Connor of Australian National University in Canberra has unearthed what it regards as the broken butt of a bone spearpoint. Three closely spaced notches, and part of a fourth, appear on each side of the artifact, above a shaft that tapers to a rounded bottom.

Wear on the notches and residue of a sticky substance close to the bottom suggest that the point was tied and glued to a slot on the side of a wooden handle or inserted into a split hollow shaft, the researchers report January 15 in the *Journal of Human Evolution*. Stone Age islanders in boats probably threw spears at large fish and other marine prey, O'Connor proposes.

Until now, comparably complex hunting weapons made on islands near Timor had been dated to no more than several hundred years ago. Curiously, 80,000- to 90,000-year-old African bone spearpoints display notches similar to those on the Timor find, O'Connor says. — *Bruce Bower*

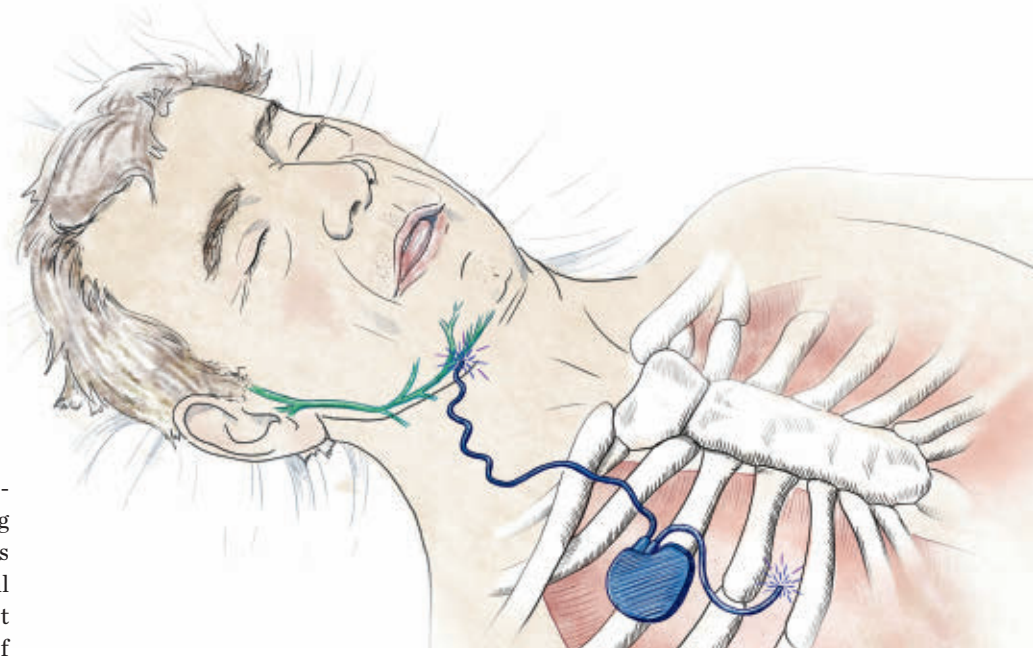
FROM TOP: JPL-CALTECH/NASA, CORNELL, ARIZONA STATE UNIV.; S. O'CONNOR

BODY & BRAIN

Pacemaker treats sleep apnea

Experimental device works for many patients who can't use breathing machines

BY NATHAN SEPPA



Breathe easy An electronic pacemaker (blue) implanted beneath the skin gets signals from a sensor between the ribs when the chest expands. The pacemaker shoots an impulse to a lead attached to the nerve (green) that controls the muscle at the tongue's base. This causes the tongue to protrude slightly, opening a person's throat for an inhale. SOURCE: P.J. STROLLO *ET AL*/*NEJM* 2014

An implantable gizmo can halt obstructive sleep apnea, a nighttime breathing disorder that disrupts rest and robs the body of oxygen. The experimental device, an electronic pacemaker that syncs breathing with the opening of the throat, relieved sleep apnea in two-thirds of people who tested it.

The volunteers had moderate-to-severe sleep apnea but couldn't tolerate standard treatment with a breathing machine that requires wearing a mask. That machine, called CPAP for continuous positive airway pressure, delivers air at a steady pace to keep airways open. Beyond CPAP, few treatments are available for severe sleep apnea, says study coauthor Ryan Soose, an otolaryngologist at the University of Pittsburgh Medical Center. "Other solutions are needed," he says, and the pacemaker "comes at it in a really unique way, mainly targeting the anatomy of the throat."

Soose and other researchers implanted pacemakers in 126 apnea patients, who were instructed to turn the devices on each night for a year. On average, patients reported substantially less daytime sleepiness than before getting the pacemaker. They had fewer sharp drops in blood oxygen per hour, a sleep test found, and struggled for breath less during sleep — dropping from a median of 29 gasps per hour to nine. The report appears in the Jan. 9 *New England Journal of Medicine*.

29
gasps of air per hour
Average rate of breathing problems before implantation of pacemaker

9
gasps of air per hour
Average rate of breathing problems after implantation of pacemaker

When the scientists randomly assigned 23 of the volunteers who had benefited from the pacemaker to get the device shut off for a week, the patients began having sleep apnea problems again.

H. Klar Yaggi, a pulmonologist and sleep researcher at the Yale School of Medicine, expects the device to succeed. "This has the potential for changing practice." He says the pacemaker's effects on breathing are comparable to CPAP's. But while CPAP remains the first-choice option for patients, Yaggi says, 40 percent use the device inconsistently or abandon it.

Surgeons implant the pacemaker beneath the skin of the upper chest. A wire extends from the device to a nearby spot between ribs, where a sensor detects the start of each breath as the chest expands. An electric signal then shoots along a wire threaded beneath the skin up to the neck to stimulate a nerve that controls tongue and throat muscles. The nerve makes the tongue stick out slightly and the throat open. In many patients, this frees up breathing.

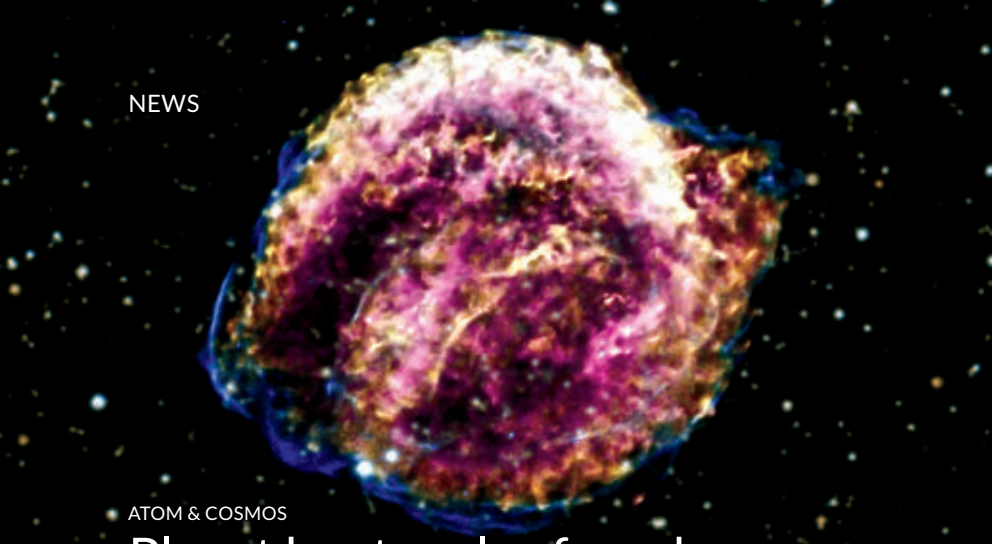
Sleep apnea carries an increased risk of stroke, high blood pressure and heart attack. In 66 percent of the volunteers, Soose says, the pacemaker reduced stoppages of breath to fewer than 20 per hour, the threshold for cardiovascular risk. About one in five reported some tongue weakness or soreness, but this went away. Two people needed to have their devices repositioned. One patient asked to have the pacemaker removed, and one died of a heart problem unrelated to the implant.

Patients in the study have been allowed to keep their pacemakers and will continue to be monitored, says study coauthor Patrick Strollo Jr., a physician and sleep researcher also at Pittsburgh. The technology comes with lithium batteries that can last six to eight years, he says. The device is made by Inspire Medical Systems in Maple Grove, Minn., which provided support for the study.

Strollo acknowledges that the participants weren't randomly selected. The study largely excluded people who were obese, had very severe or very mild sleep apnea or had large tonsils. The study also didn't compare the pacemaker with other sleep therapies.

The pacemaker is unlikely to get tested against sham surgery — the equivalent of a placebo — because sleep apnea is too serious to leave untreated, says Atul Malhotra, a pulmonologist at the University of California, San Diego. But, he says, the study "does set the stage for a comparative-effectiveness study against CPAP." ■

NICOLLE RAGER FULLER



ATOM & COSMOS

Planet hunter also found supernovas

Now-defunct telescope captured five stellar explosions

BY ANDREW GRANT

OXON HILL, MD. — NASA's premier planet-hunting telescope had another talent: spotting the cataclysmic demise of massive stars. The Kepler space telescope detected at least five supernovas, giving astronomers a rare look at these calamitous explosions from the start.

From May 2009 until May 2013, when a critical piece of equipment failed (*SN: 9/21/13, p. 18*), the Kepler telescope found at least 3,500 likely planets orbiting other stars. The telescope stared continuously at a single patch of sky, measuring stars' brightness every 30 minutes. Occasionally the scope detected subtle dips in stars' brightness, revealing that planets had crossed in front of them and cast shadows.

In late 2009, astronomer Rob Olling of the University of Maryland in College Park began to wonder what Kepler could do if it stared at galaxies. Like stars, galaxies shine with relatively consistent brightness. But if a massive star exploded, a galaxy's brightness would soar. After Olling and Maryland colleagues Richard Mushotzky and Ed Shaya submitted a proposal to the Kepler team, the telescope began monitoring 400 galaxies within its field of view.

Kepler data revealed at least five and as many as eight supernovas over a two-year period, Olling reported January 8 at a meeting of the American Astronomical Society. In some ways, the data are rudimentary: They consist only of brightness measurements, so astronomers can't figure out details such as the supernovas' structures and the chemical composition of the shrapnel. And Kepler beamed data to Earth only once every 90 days. Because supernovas fade away after several weeks, astronomers couldn't point other telescopes at the supernovas that Kepler identified.

New data from the Kepler space telescope shed light on what sets off explosions known as type 1a supernovas (one shown).

Yet no other telescope has chronicled a supernova so meticulously, from the first signs of explosion through its peak and dimming. Prior studies have analyzed the origins of supernovas by studying sky images taken just before and after a supernova appeared (*SN: 3/9/13, p. 16*). "It's really neat because Kepler is observing the star already, before it explodes," said Nathan Smith, an astronomer at the University of Arizona in Tucson. "Then [Kepler] sees the supernova immediately and watches it brighten."

At least two of the supernovas are type 1a, the most commonly detected variety. Astronomers think that type 1a explosions are triggered by the collision of an unknown type of star with a white dwarf, the Earth-sized corpse of a star like the sun. If the first star is large, then its surface should glow in the explosion's blast wave, well before the supernova reaches peak brightness. However, Kepler found no such initial glow, which suggests that the colliding object is relatively small, perhaps another white dwarf. ■

BODY & BRAIN

Migraines respond to great expectations

Meds and placebos both fight pain better when patients anticipate getting real drug

BY BRUCE BOWER

When it comes to pain, what migraine-headache sufferers think about their pills' identities matters nearly as much as whether or not those pills contain active medication, a new study suggests.

Migraine meds labeled as placebos dull headache pain less effectively than the same pills identified either as the real deal or as possibly a genuine drug, say neuroscientist Rami Burstein of Harvard Medical School and colleagues. Placebo pills given to migraine patients worked the same way, easing headache pain better when labeled as definitely or possibly containing active medication,

EARTH & ENVIRONMENT

Trees' growth keeps climbing with age

Oldest specimens pack on weight fastest, making them excellent carbon collectors

BY MEGHAN ROSEN

As trees grow older and bigger, they bulk up faster and faster, researchers report January 15 in *Nature*.

The findings revise scientists' understanding of big trees' role in stockpiling carbon drawn from the air.

"This will come as a surprise for many people," says Maurizio Mencuccini, an ecologist at the University of Edinburgh. "The basic perception is that trees are less capable of growing as they age."

For years, many scientists believed that trees' growth was quick in the

X-RAY: CXC/NASA, D. PATNAUDE/SAO; OPTICAL: DSS

the researchers report in the Jan. 8 *Science Translational Medicine*.

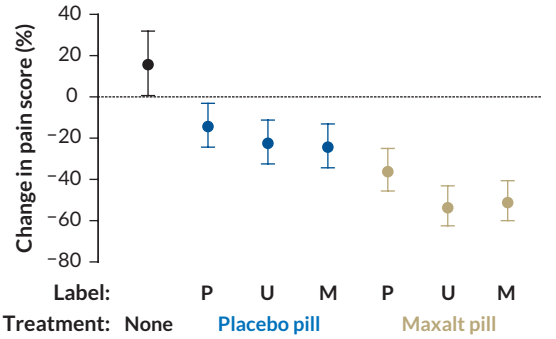
Placebo pills mislabeled as the migraine drug Maxalt provided close to as much pain relief as Maxalt mislabeled as a placebo. "The physiological effects of the drug and the psychological effects of a placebo contributed almost equally to the therapeutic efficacy of the migraine treatment," Burstein says.

He suspects that physicians who equivocate about Maxalt's pain-fighting power with statements such as, "Let's give the drug a try and see if it works," end up lowering patients' expectations. As a result, patients don't experience as much pain relief as they potentially could.

Burstein's group also found that patients who took accurately labeled placebos reported more pain relief than those receiving no treatment. The ritual of pill taking by itself may help treat migraines, the scientists suggest.

The study is one of only a few to demonstrate that a patient knowingly getting a placebo can experience "an actual effect superior to not receiving a treatment," says physician Damien Finniss of the University of Sydney.

Names count In a new study, migraine patients experienced the greatest decline in pain when placebo pills (blue) and Maxalt pills (brown) were labeled as "Maxalt" (M) or "Maxalt or placebo" (U). Pills labeled "placebo" (P) were the weakest painkillers in each treatment condition. Between 30 minutes and 2.5 hours after an attack started, migraine pain increased among patients who got no treatment at all (black).



Burstein's group recruited 66 patients who experienced recurring migraine headaches. Patients recorded pain scores 30 minutes and 2.5 hours after an untreated migraine attack. In six ensuing attacks, each participant did the same but took Maxalt at the 30-minute mark of three episodes and a placebo at the same point in three other headache bouts. Each treatment was alternately labeled as "placebo," "Maxalt or placebo" and "Maxalt."

A 2001 study led by neuroscientist Fabrizio Benedetti of the University of Turin Medical School in Italy similarly observed that a saline solution described to patients as a powerful painkiller produced more pain relief than an accurately portrayed saline solution did for other patients. A third group receiving a saline drip depicted as a possible painkiller reported levels of pain relief in between those of the other groups.

Each migraine patient in the new study took a drug and a placebo labeled in three different ways, an improvement in research design over his own group's investigation, Benedetti says. ■

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beginning and tapered off in old age. But the evidence for this pattern is mostly indirect, says study coauthor Nathan Stephenson, an ecologist at the U.S. Geological Survey in Three Rivers, Calif.

In a forest with trees of the same age, scientists have found that productivity — the mass of all the limbs, branches and trunks in a forest — tends to decline over time. And the leaves of big, old trees don't convert sunlight into sugar as well as the leaves of small, young trees do.

Big, old trees such as this *Shorea smithiana* tend to grow faster than smaller, younger ones. Older trees may capture more atmospheric carbon than scientists had thought.

"The in-between scale — the individual tree — has tended to be ignored," Stephenson says.

Though some researchers have suggested that trees' growth rate increases continuously rather than declining, until now no one had examined a large collection of individual trees. So Stephenson and colleagues measured the diameters of thousands of trees in California's Sierra Nevada mountains and teamed up with other scientists who had collected similar measurements on forested continents around the world. The researchers estimated the growth rate of each tree from two measurements, taken on average five to 10 years apart.

All together, Stephenson's group calculated growth rates for 673,046 trees from 403 species. In 87 percent of the species, bigger trees tended to pack on the pounds more quickly than smaller trees. The productivity drops that researchers have seen in aging forests may be due to older trees dying off, Stephenson says.

Big, old trees are already known as carbon reservoirs. But since trees use carbon to grow, the new findings suggest that these trees may be active carbon-sucking sponges too. If forests were sports teams, Stephenson says, "the star players would be the 90-year-olds."

Ecologist Yude Pan of the U.S. Department of Agriculture Forest Service in Newtown Square, Pa., says the new work "might help us to appreciate those bigger trees and to conserve them."

But a booming growth rate doesn't necessarily reflect high carbon intake, says forest ecologist Frida Piper of the Center for Ecosystems Research in Patagonia in Coyhaique, Chile. Old trees could be stocking less carbon in their roots. "We need to know what's happening below ground level," she says. ■

FROM TOP: ADAPTED FROM S. KAM-HANSEN *ET AL*/*SCIENCE TRANSLATIONAL MEDICINE* 2014; SABRINA RUSSO

GENES & CELLS

Stone Age Spaniard had blue eyes

Blue eyes may have evolved before blond hair and pale skin, a genetic analysis of a 7,000-year-old hunter-gatherer's skeleton suggests. The skeleton was found in 2006 in a cave at Spain's La Braña-Arintero archaeological site. DNA from one of the skeleton's teeth shows that the man, called La Braña 1, is genetically different from most present-day Europeans, Carles Lalueza-Fox of the Institute of Evolutionary Biology in Barcelona and colleagues report January 26 in *Nature*. La Braña 1's eyes were blue (or at least not brown), but his hair and skin were dark, the researchers determined from the skeleton's pigment genes. — *Tina Hesman Saey*

MATTER & ENERGY

Glass stops cracks in their tracks

Carving squiggly lines into glass can actually toughen it up. The new engraving technique could keep wine glasses, windowpanes and medical implants from shattering. It might even beef up bulletproof glass. Ordinary bulletproof glass relies on a sandwich of glass, plastic and a rubbery glue called polyurethane to absorb the impact of speeding projectiles. Francois Barthelat and colleagues at McGill University in Montreal instead laser cut a wavy pattern of tiny holes into glass microscope slides and then filled the holes with polyurethane. Just as paper rips along a perforated line, the etched glass cracked along the patterns when researchers stressed it. But the curvy patterns lock the glass together like puzzle pieces. These interlocking pieces absorb energy, so a crack that would normally zip through the brittle material petered out instead, the team reports January 28 in *Nature Communications*. Biology inspired the researchers to strategically position weak spots that guide cracks to tough-to-break areas, Barthelat says: "This kind of trick is used in bones, teeth and seashells." — *Meghan Rosen*

LIFE & EVOLUTION

Swimming dolphins don't cheat

Dolphins generate thrust just fine and have no need to compensate for supposedly underpowered muscles, a study of dolphin swimming finds. The study contradicts a 1936 paper by Sir James Gray, who calculated that dolphins don't have the muscle to produce the thrust they need to swim as fast as they do. Called Gray's paradox, the work raised hopes of using dolphins' tricks to improve torpedoes (and swimsuits). Scientists hypothesized that dolphins somehow reduce drag by creating smooth, laminar flow in water rushing by their skin instead of the usual turbulent flow. By filming bottlenose dolphins swimming through a curtain of tiny air bubbles, Frank Fish of West Chester University in Pennsylvania and colleagues used the frame-to-frame shifts in bubble position to work out how much thrust the dolphins produced. A dolphin's flukes generate high thrust and power without special drag-reducing tricks, the team reports January 15 in the *Journal of Experimental Biology*. So there's no need for a "paradox." — *Susan Milius*

BODY & BRAIN

Small fetal size early on may bring health risks later

Poor fetal growth in the first trimester is associated with cardiovascular risk factors in childhood, researchers report. While far from conclusive, the finding suggests that impaired early fetal growth — even before a woman knows she is pregnant — might have long-term consequences. Researchers at Erasmus University in the Netherlands calculated the conception dates for 1,184 women. The team then used ultrasound to measure the length of each fetus at the end of the first trimester and identified fetuses in the bottom and top one-fifth. Later, the researchers examined the women's children at a median age of 6 years. Poorer growth during early pregnancy was linked to greater total fat mass, higher diastolic blood pressure (the "bottom" number), more abdominal fat and higher cholesterol, the scientists report January 23 in *BMJ*. The trends held after researchers accounted for differences in the moms, including duration of breast-feeding. — *Nathan Seppa*

ATOM & COSMOS

Clouds on brown dwarf mapped

One of the first maps of clouds on an object outside the solar system appears in the Jan. 30 *Nature*. The clouds surround Luhman 16B, a brown dwarf just 6.5 light-years away in the constellation Vela. Brown dwarfs are gaseous objects larger than planets but too small to fuse hydrogen as true stars do. Previous studies hinted that brown dwarfs' ultrahot atmospheres contain clouds of molten iron and silicates. A team led by Ian Crossfield of the Max Planck Institute for Astronomy in Heidelberg, Germany, used the Very Large Telescope in Chile to gather infrared light as Luhman 16B rotated on its axis. Darker areas on the brown dwarf indicated higher, colder clouds (but still hot enough to melt iron) and lighter patches indicated either lower, hotter clouds or hydrogen gas on the dwarf's surface, visible through gaps in the upper layer. The team saw cloudy and clear patches lasting roughly five hours, which is the length of one day on Luhman 16B. — *Gabriel Popkin*

SKULL: J.M. VIDAL ENCINA; ILLUSTRATION: CSIC

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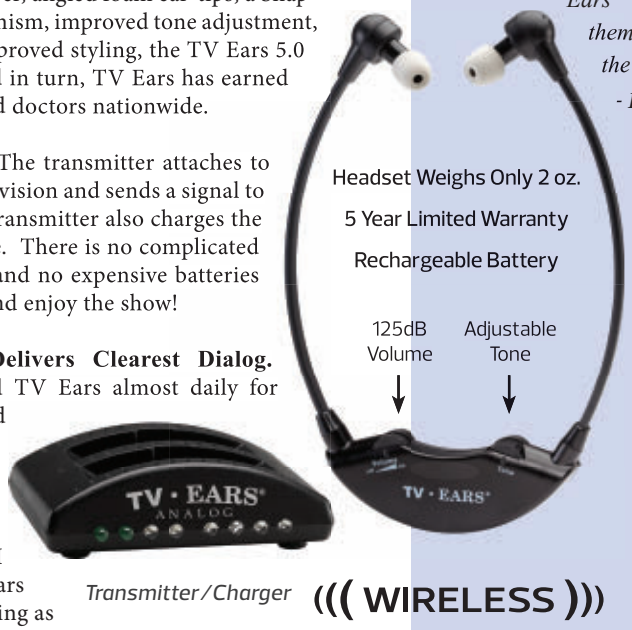

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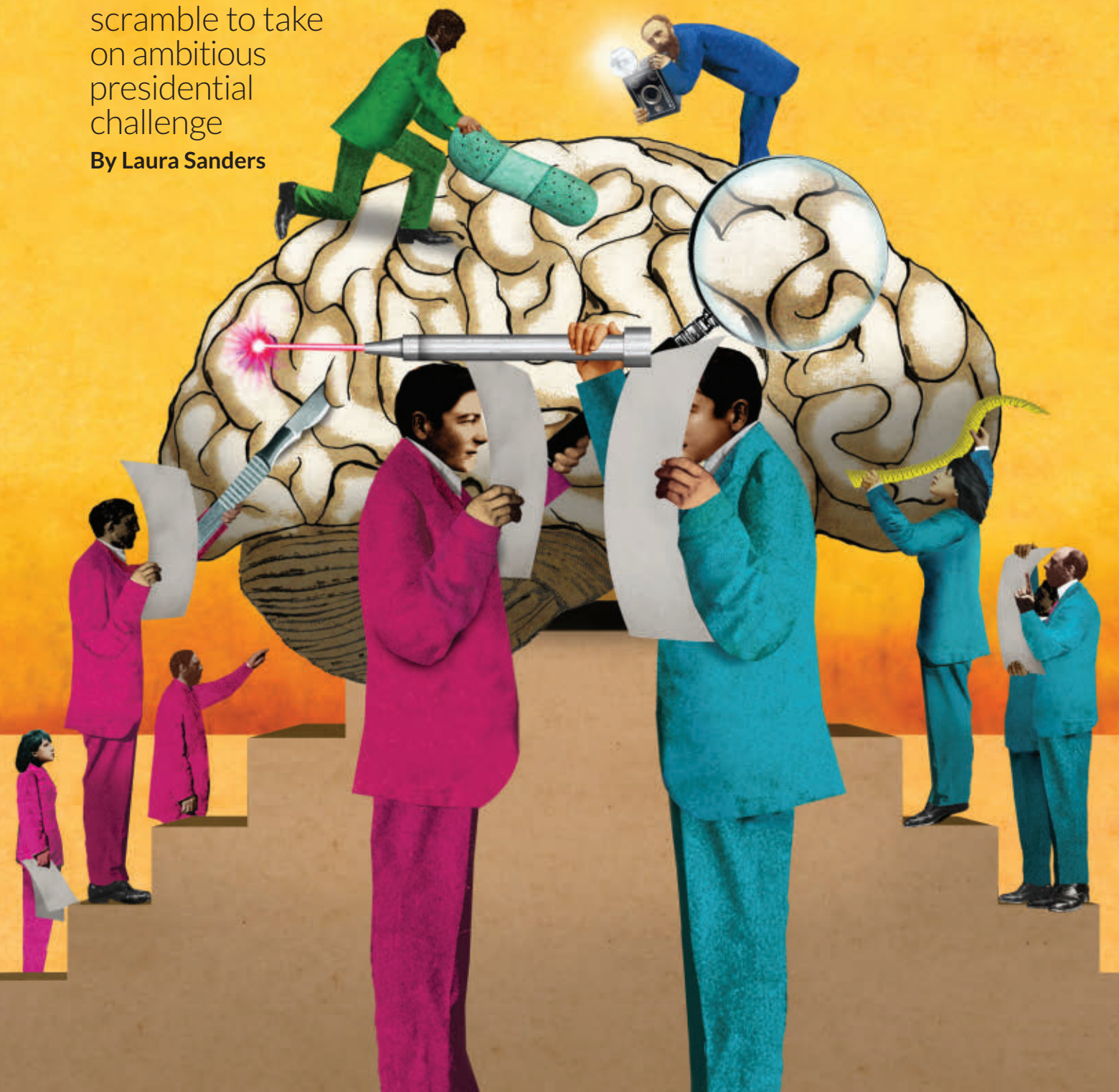
Brain Shot

Neuroscientists scramble to take on ambitious presidential challenge

By Laura Sanders



When the president of the United States makes a request, scientists usually listen. Physicists created the atomic bomb for President Roosevelt. NASA engineers put men on the moon for President Kennedy. Biologists presented their first draft of the human genetic catalog to an appreciative President Clinton.

So when President Obama announced an ambitious plan to understand the brain in April 2013, people were quick to view it as the next Manhattan Project, or Human Genome Project, or moon shot.

But these analogies may not be so apt. Compared with understanding the mysterious inner workings of the brain, those other endeavors started with an end in sight.

In a human brain, 85 billion nerve cells communicate via trillions of connections using complex patterns of electrical jolts and more than 100 different chemicals. A pea-sized lump of brain tissue contains more information than the Library of Congress. But unlike those orderly shelved and cataloged books, the organization of the brain remains mostly indecipherable, concealing the mysteries underlying thought, learning, emotion and memory.

Still, as with other challenging enterprises prompted by presidential initiatives, success would change the world. A deep understanding of how the brain works, and what goes wrong when it doesn't, could lead to a dazzling array of treatments for brain disorders — from autism and Alzheimer's disease to depression and drug addiction — that afflict millions of people around the world.

That's why President Obama threw his weight behind the BRAIN Initiative, short for Brain Research through Advancing Innovative Neurotechnologies (*SN: 5/4/13, p. 22*). The premise is simple: Before doctors can fix the brain, scientists must first understand how it works. And to understand how it works, scientists need tools to study it. With $110 million of federal funding in its first year, the BRAIN Initiative is intended to spur scientists to develop new technologies to measure and manipulate the brain. Eventually, if it is to join the list of presidential science successes, the project will catalog all the brain's parts and processes, explore how cells and molecules create thought and behavior, and build powerful new weapons for neutralizing the pathological enemies of the brain and mind.

Yet even aside from those scientific challenges, which are all huge in their own right, the project faces many major logistical hurdles.

Manhattan Project
1942–1945

Goal: To develop the world's first nuclear weapon, an atomic bomb, during World War II

Cost:
$26 billion*

People involved:
>100,000

Apollo Program
1963–1972

Goal: To land Americans on the moon before 1970

Cost:
$134 billion*

People involved:
>400,000

Human Genome Project
1990–2003

Goal: To map out the 3 billion chemical "letters" of DNA in the human genome

Cost:
$4.6 billion*

People involved:
Thousands

BRAIN Initiative
2014–?

Goal: To develop new technologies for mapping the human brain's cells and circuitry; discover the neural and molecular basis of learning, thought and memory; and develop methods of prevention and more effective therapies for brain disorders

Initial cost:
$110 million**

People involved:
Not yet known

**In 2013 dollars*
***Federal funding for 2014*

It's not clear, for instance, how various government agencies and private institutions involved in the project will coordinate their efforts. Nor is it clear how the BRAIN Initiative will relate to the European Union's $1.3 billion Human Brain Project. Some scientists say the BRAIN Initiative's initial funding is too paltry to make real progress and that future funding is a political uncertainty.

Perhaps most unsettling, the BRAIN Initiative has no definitive goal. Unlike mushroom clouds, a collection of moon rocks or the software for a human being, the BRAIN project envisions no tangible result, many scientists say. "It isn't clear what victory will look like on this project," says Thomas Insel, director of the National Institute of Mental Health in Bethesda, Md. "I think people have to be comfortable with that."

Despite these caveats, though, many neuroscientists appreciate that President Obama's announcement elevated the status of brain research and captured the attention of their community. "When the president says it, people listen up," says Christof Koch of the Allen Institute for Brain Science in Seattle. "I think that, by itself, is a very important thing. It really shows that neuroscience has come of age."

Ambitious goals

While the BRAIN Initiative's objectives are hard to express in concrete terms, the project is full of visionary promise. "The ultimate goal is to understand who we are," says Terry Sejnowski of the Salk Institute for Biological Studies in La Jolla, Calif. "How is it that our brain is able to look out into the world and see things? How is it that we are able to make decisions? How is it that we're able to coordinate enormous amounts of knowledge?"

The people charged with translating these esoteric goals into concrete action are beginning to define their task more precisely. But there is no consensus on how to proceed. With no central organizing entity, the three government agencies participating — the National Institutes of Health, the Defense Advanced Research Projects Agency and the National Science Foundation—interpret the BRAIN Initiative's mission in their own ways. So do the private organizations involved, including the Salk Institute, the Allen Institute, the Kavli Foundation and the Howard Hughes Medical Institute's Janelia Farm campus in Ashburn, Va.

The NIH, which is putting up $40 million in funding for fiscal year 2014, has taken a methodical approach by first appointing a committee of

OPPOSITE PAGE: MICHAEL MORGENSTERN; THIS PAGE: E. OTWELL

16 neuroscientists. That group, headed by William Newsome of Stanford University and Cornelia Bargmann of the Rockefeller University in New York, spent the summer of 2013 in four workshops talking with neuroscientists about what ought to be included in the initiative.

In September, the committee released a preliminary report describing nine priorities. They were extremely ambitious. For instance, the NIH panel wants a census of all the different types of brain cells and a description of how nerve cells, or neurons, collectively give rise to behavior. Powerful new technology also features prominently on the wish list. One of the goals calls for developing tools capable of producing anatomical maps of the human brain with unprecedented clarity.

Further priorities include developing techniques that can eavesdrop on many neurons at the same time and allow scientists not just to listen in, but to change how those neurons behave. To make sense of all of this data, the report calls for improved theoretical, statistical and modeling approaches.

Each of these goals on its own could easily take years or even decades to accomplish. For the final report, the goals, milestones and timeline will be sharpened, says Sejnowski, a member of the working group.

Like NIH, DARPA also emphasizes new tools, but with a much more targeted goal in mind for its $50 million investment in 2014: healing soldiers. "We serve a constituency" — the active duty service member — says Geoffrey Ling, deputy director of the Defense Sciences Office. "And the active duty service member right now has got a lot of issues medically."

Currently, more military members die from suicide than from direct combat injury, says Ling. "And that's the tip of the iceberg." DARPA interprets its role in the BRAIN Initiative as alleviating some of the pernicious mental health problems that plague service members.

In October and November, DARPA announced two projects. One, called SUBNETS (for Systems-Based Neurotechnology for Emerging Therapies), seeks new ways to record neural activity from and stimulate the brains of people with post-traumatic stress disorder, anxiety disorder, traumatic brain injury and other diseases. DARPA envisions a device that both diagnoses and treats mental health problems, first by listening for abnormal electrical signals and then correcting them. For success, the project will need engineers to build new medical devices, computational neuroscientists to develop theories about how neurons transmit information and clinicians to test the prototype in people.

The second project, called RAM (for Restoring Active Memory), aims to develop an implantable brain device that will help restore lost memories to soldiers or veterans. Devised by Ling, the project plans to move from idea to device quickly. "Our timeline is four to five years, and we're not joking," he says.

Seeking new tools

Achieving such ambitious goals — figuring out how neurons create behavior, curing mental illness and restoring lost

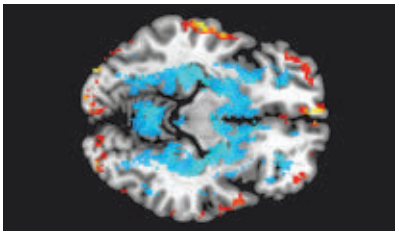
FROM LEFT: Y. KANEONKE *ET AL*/*PLOS ONE* 2012; LABORATORY OF NEURO IMAGING/UCLA; KWANGHUN CHUNG & KARL DEISSEROTH/HHMI, STANFORD UNIV.

Brain technology

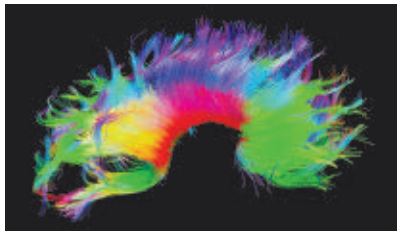
President Obama's BRAIN Initiative seeks a comprehensive understanding of how molecular and electrical processes orchestrated by nerve cells produce the brain's ability to think, learn and control behavior. A central part of the initiative focuses on the need to improve existing technologies and to develop new ones that probe the brain's inner workings on smaller and smaller scales.

Old tech

Two techniques using magnetic resonance imaging, or MRI, have already made progress in mapping the physical connections (fibers of white matter) linking various parts of the brain and in identifying regions that are active during specific tasks.



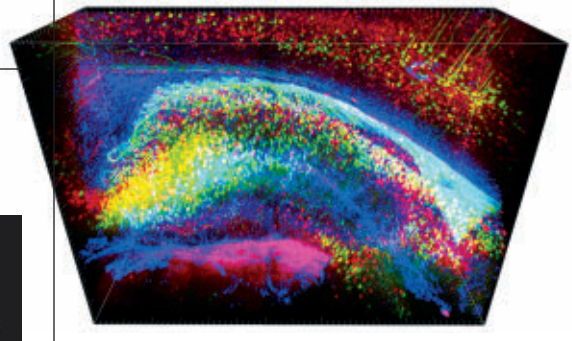
Functional MRI records activity in different brain areas by tracking the flow of blood and its oxygen content. Active brain cells require more blood to provide oxygen. fMRI signals show which parts of the brain are at work during certain tasks or behaviors.



Diffusion tensor imaging maps white matter fibers by measuring the diffusion of water. The diffusion rate is faster parallel to fibers than perpendicular; mathematical analysis of the flow rate in various directions (using quantities called tensors) allows reconstruction of fibers' locations.

New tech

Several novel technologies have been developed or proposed to acquire even more detailed data about how the regions and even individual cells of the brain do their jobs.



CLARITY, short for Clear Lipid-exchanged Anatomically Rigid Imaging/immunostaining-compatible Tissue Hydrogel, replaces fat cells in the brain with a clear gel, allowing neurons to be illuminated. By infusing a brain with a liquid that eventually hardens into a gel, scientists can see previously hidden structures deep within the brain. Already, CLARITY has been used to see nerve fibers and connections in a mouse brain, and even individual neurons in a human brain that had been preserved in formaldehyde for six years.

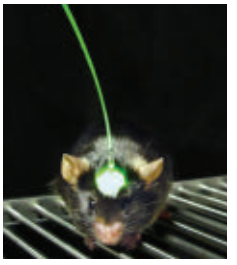
memory — is not possible with today's technology. Even though scientists have made huge leaps in their ability to listen to and manipulate neurons, current methods are still far from where they need to be.

"The tools have to be the focus," says Sejnowski. "We have to get those tools in place. There's no way of even getting off the ground until we have those tools."

NIH's initial plans reflect that belief. On December 17, the agency released six calls for projects to fund as part of the BRAIN Initiative. Each describes a tool-building plan. "What we're trying to do is get the tools and infrastructure in place so we can get a much deeper understanding of how the brain works in both health and disease," Insel says.

Scientists want to monitor the electrical and chemical behavior of many neurons — thousands or even millions — at the same time, while being able to zoom in to see and even manipulate those cells. One of today's common ways to eavesdrop on neuron behavior relies on electrodes designed decades ago. Neuroscience is still stuck using technology from the 1950s, Insel says, "while the rest of the world has learned how to go wireless and miniaturized."

Magnetic resonance imaging, or MRI, allows scientists to get good anatomical maps of the whole brain and broad activity patterns (*SN: 12/19/09, p. 16*). But as good as it is, MRI technology still misses lots of detail. A million neurons can reside in a single voxel, the smallest unit that functional MRI can detect. "MRI shows you wonderful neuroanatomical details,



In optogenetics, scientists use light to manipulate brain cells that have been genetically modified to respond to light. While already producing useful findings in animals such as mice, optogenetics would not be practical in people.

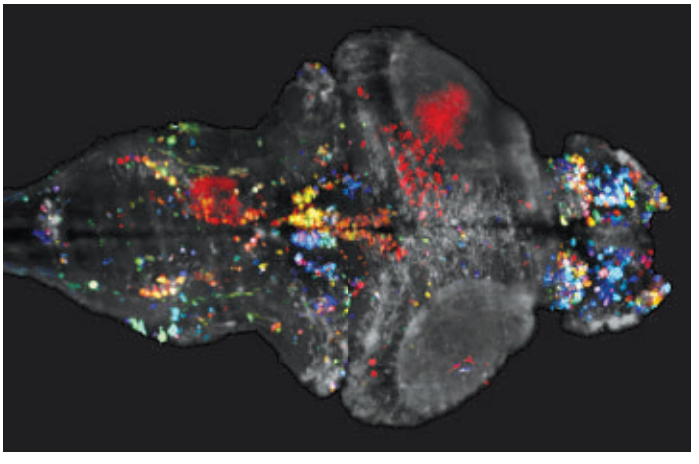
fantastic, but it does have a resolution limit," Ling says. "How can we increase it? Easy — build a bigger magnet. Oh, good, let's have a 50 Tesla magnet. What city are you going to put this in? Because you have to wipe out about seven blocks to do it." Supersizing existing technology won't work, Ling says. Fundamentally new ideas are needed.

Radically new approaches will also be needed to enable precise control of neurons' behavior. One powerful new technique, called optogenetics, lets researchers use light to control certain brain cells in animals. But it's not feasible in people, because it requires genetic alterations to make neurons produce specialized light-sensitive proteins. For now, scientists are forced to rely on less precise methods to change the activity of human neurons.

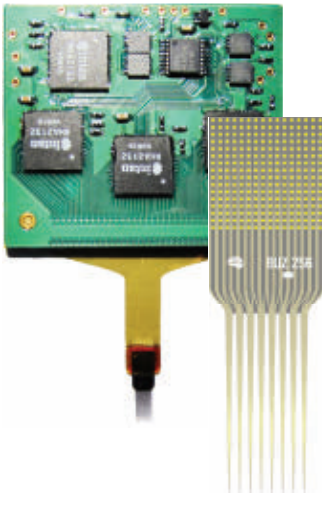
Psychiatric drugs can alter neuron behavior, for instance, but the results are imprecise, like dousing the entire engine of a car with oil. Every cell in the brain gets dosed, when only a select few actually need the drugs. What's more, in most cases scientists still don't understand how psychiatric drugs work.

A different, drug-free approach may work better: newer

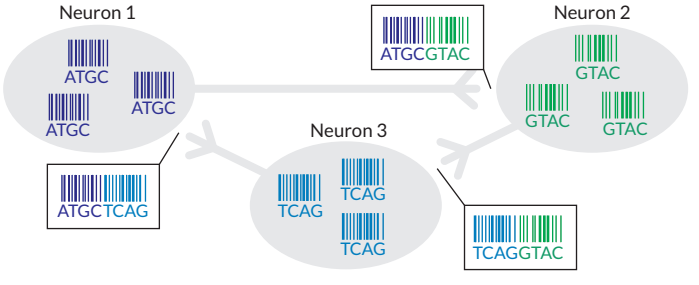
CLOCKWISE FROM TOP: INBAL GOSHEN & KARL DEISSEROTH; GYORGY BUZSAKI LAB/NYU; E. OTWELL; PHILIPP KELLER & KRISTIN BRANSON/JANELIA FARM RESEARCH CAMPUS



GCaMP is a protein that labels active neurons in the whole brain. Designer proteins can sense when nerve cells are active and change color as a result. Calcium ions that are present when a neuron fires change the shape of GCaMP proteins, causing them to fluoresce and creating a beacon that can be detected by sensitive microscopes. Scientists have used these proteins to watch the behavior of more than 80 percent of all neurons in the brain of a zebrafish larva.



Mini electrodes For decades, scientists have used electrodes to eavesdrop on neurons. But those electrodes are limited in their ability to record many neurons at one time. Scientists and technology companies are working to make smaller, more accurate electrode arrays that can both accurately detect and change the behavior of hundreds or thousands of neurons at once.



DNA tagging By labeling each neuron with a DNA bar code, scientists can reconstruct the physical connections between neurons quickly and cheaply. So far, this method has been used to reconstruct all the connections between cells in a dish.

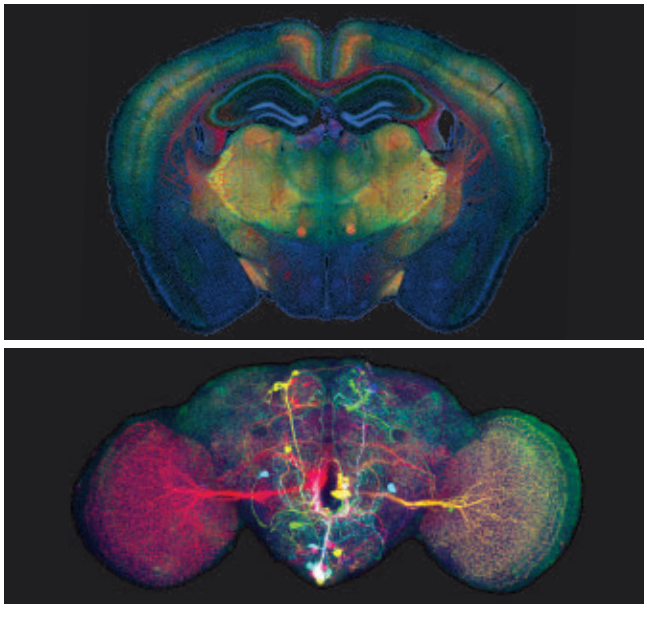
technology called deep brain stimulation. It serves as a brain pacemaker. By zapping neural highways with electrodes implanted in the brain, deep brain stimulation has shown promise for treating people with Parkinson's disease and severe depression. And yet, as with psychiatric drugs, the technique is still imprecise and not well understood.

"I think people understand that you're not going to be able to fix something as complicated as the brain with the current tools. They're too crude," Sejnowski says, like "trying to fix a computer with a wrench."

Instead of more wrenches, scientists need powerful precision tools, some of which are in the works. The Allen Institute, HHMI and others have partnered with a nanoelectronics research center called imec to build tiny but powerful electrodes that can record the behavior of hundreds of neurons with great accuracy. "That's going to be pretty awesome technology," Koch says.

Scientists at Janelia Farm are devising intricate ways to illuminate neural behavior in zebrafish, flies and mice. By genetically engineering neurons to produce a protein called GCaMP, the researchers can watch each individual neuron fire off a message. The concept of using proteins to detect neuronal activity isn't new, but the sensitivity of this latest version is much better than previous attempts, says Gerald Rubin, Janelia Farm's executive director. It awed many in the field in March 2013 when the Janelia Farm researchers circulated a movie of zebrafish brain activity.

Scientists are also making progress on mapping the connections between neurons. Most attempts rely on powerful microscopy (*SN: 6/15/13, p. 20*). But there might be a better way, says Anthony Zador of Cold Spring Harbor Laboratory in New York.



One organization working with the BRAIN Initiative, the Allen Institute for Brain Science, has been developing an atlas of connections in the mouse brain (top). Scientists at the Howard Hughes Medical Institute's Janelia Farm campus have been probing the brain of fruit flies (bottom).

Instead of using microscopes, Zador and colleagues are attempting to attack the problem with DNA sequencing, which is cheap and reliable. Their method relies on using genetic tricks to tag neurons with unique chains of DNA. By analyzing how those DNA tags mingle at synapses — the communication connections between neurons — a computer could reconstruct all of the physical connections in a brain. So far, the team has had success only in cells in a dish. If the technique works in animals, figuring out every single synapse in the entire mouse cortex will cost just a few thousand dollars, Zador estimates.

Making the vision real

If the BRAIN Initiative serves as an incubator for the next great brain technology, the payoff would be huge, Newsome says. The ability to record the behavior of tens of thousands of neurons simultaneously, map the connections between those neurons and then manipulate those neurons, all in a fully awake behaving animal, or person, "is not something that neuroscience has ever been able to contemplate in its history," says Newsome. "It's kind of a breathtaking vision."

Success in realizing that vision, though, will mean that neuroscientists have to face a big shift in how they do their work.

As neurotechnology improves and produces ever more massive piles of complicated data, neuroscientists will need to know more about statistics, engineering and computational biology. To succeed, the BRAIN Initiative will need to bring together experts in all these different fields. It will also need neuroscientists to coordinate their efforts and share their data freely. "We are going to have to reorganize the way people do their research," Sejnowski says. The same goes for the nongovernmental agencies working on the BRAIN Initiative.

Currently no one agency or person is in charge of the initiative. Such decentralization might make swift progress, without duplication of effort, difficult. Although the three government agencies involved — DARPA, NIH and NSF — have been aware of what the others were doing, they haven't merged their differing priorities. "We're all so busy getting these projects launched, I don't think we've had a lot of time to think about how they're going to be integrated," Insel says.

The private groups, referred to by the White House as BRAIN Initiative "partners," set their own course and spend their own money as they see fit. Because the goals of the Allen Institute, the Salk Institute and Janelia Farm align closely with federal goals, these institutes don't anticipate changing their previously set research agendas.

"Partnership is a funny word," says Janelia Farm's Rubin. In a sense, Janelia Farm is a partner, he says, because it is putting up a big chunk of money — $30 million annually — toward projects that dovetail with the BRAIN Initiative. Much of that research focuses on how information in the fruit fly brain is stored and processed. "But we're not a partner in the sense that we're getting together at a big table with NIH folks and NSF and DARPA and deciding what the goals are and then collectively deciding what we're doing," Rubin says.

FROM TOP: COURTESY OF THE ALLEN INSTITUTE FOR BRAIN SCIENCE; COURTESY OF THE SIMPSON LAB/JANELIA FARM RESEARCH CAMPUS

Likewise, Koch says that the Allen Institute has been working on most of the questions the NIH group came up with. "We are fulfilling already a part of the BRAIN Initiative mission," he says. Allen Institute scientists have been building detailed maps of the mouse brain, which could help efforts to understand how the human brain works.

Aside from the privately funded research that is already under way, major new BRAIN Initiative research will require new federal money. And so far, the new money has been scant. In 2014, NIH is contributing $40 million to the BRAIN Initiative, less than 1 percent of the $5.7 billion that the agency spends on neuroscience research each year. In 2014, DARPA will spend $50 million on its newly announced projects, and NSF will spend $20 million on relevant projects already in progress.

Although to many scientists, the BRAIN Initiative's preliminary pot seems small, that money is a down payment, Insel says, meant to get the ball rolling in the hope that Congress will provide more support for the project.

Of course, to help sell the project to politicians who vote on budgets (or as has recently been the case, don't vote on budgets), scientists need a tagline, a slogan, a simple way to encapsulate the importance of the BRAIN Initiative. So far, there is no such thing.

"We've talked and thought about that a lot in the committee," Newsome says. But the group couldn't come up with a pithy way to capture the project's essence. "That question, it's a real tension. To what extent do we try to depict this as an Apollo-like project or a genome-like project, in which case you have a tagline and a particular deliverable you're looking for? Or to what extent do you acknowledge that this is a more open-ended kind of project?"

The sell is important, says Zador. In the current economic squeeze, funding must be justified to politicians and the public. If the BRAIN Initiative underdelivers, people will be disappointed.

Instead of a promise to cure brain disease, or unlock the mysteries of memory, emotion and thought, perhaps the brain project is best described as a wedge, says Sean Eddy of Janelia Farm. With its emphasis on sophisticated tools, the project promises to pry open an entirely new realm of neuroscience research, Eddy wrote last April in *Current Biology*, enabling countless labs around the world to make discoveries in their small corner of the brain.

This vision of the initiative's success, in which thousands of neuroscientists storm the inhospitable terrain of the brain armed with an awe-inspiring new arsenal of tools, is staggering. Compared with any other project President Obama could have backed, the brain is the most worthy, Eddy says. "This is it."

If the project flops, scientists will still learn a lot in the attempt. If the project succeeds, the benefits are almost unimaginable. Clinicians might be able to neutralize — or even prevent — devastating disorders such as autism, Alzheimer's disease and traumatic brain injury. Computers could become ever more powerful by cribbing from the brain's operating system. Classrooms, military training camps and courtrooms could be optimized to play to the strengths of the human brain and protect it from its weaknesses. These are among the motives that drive neuroscientists, and for all its shortcomings, the BRAIN Initiative has already succeeded in getting people dreaming about what might be possible.

"I can't tell you where we're going to be two years from now," Sejnowski says, "but I can tell you that it'll be far ahead."

Priorities for the BRAIN Initiative

In response to President Obama's call for a major new initiative to understand the brain, the National Institutes of Health organized a committee to articulate a list of priorities. The group identified nine, briefly summarized here:

1. Generate a census of cell types
Characterize all cell types in the nervous system and develop tools to observe and manipulate them.

2. Create structural maps of the brain
Map connected neurons in local and distributed circuits in order to understand the relationship between neuron structure and function. Create tools to reconstruct anatomy of neural circuits at all scales and identify circuit inputs and outputs.

3. Develop new large-scale network recording capabilities
Record neuron activity from complete networks over long time periods in all brain areas with the use of improved existing technologies and entirely new technologies.

4. Develop a suite of tools for circuit manipulation
Activate or inhibit activity in neuronal circuits, using optogenetic, pharmacological, biochemical and electromagnetic tools.

5. Link neural activity to behavior
Understand the neural basis for cognition and behavior, using technologies that can precisely observe behavior under a broad set of conditions while measuring and manipulating neuron activity.

6. Integrate theory, modeling, statistics and computation with experimentation
Apply theory and statistics to understand complex brain functions where human intuition fails, using new methods for mining, analyzing and interpreting data.

7. Delineate mechanisms underlying human imaging technologies
Improve spatial and time resolution of human brain imaging techniques while developing a better understanding of the cellular mechanisms underlying the signals used to compose images.

8. Create mechanisms to enable collection of human data
Develop high ethical standards for clinical care research while developing methods to maximize the collection of beneficial information from humans undergoing diagnostic brain monitoring or receiving neurotechnology for clinical applications.

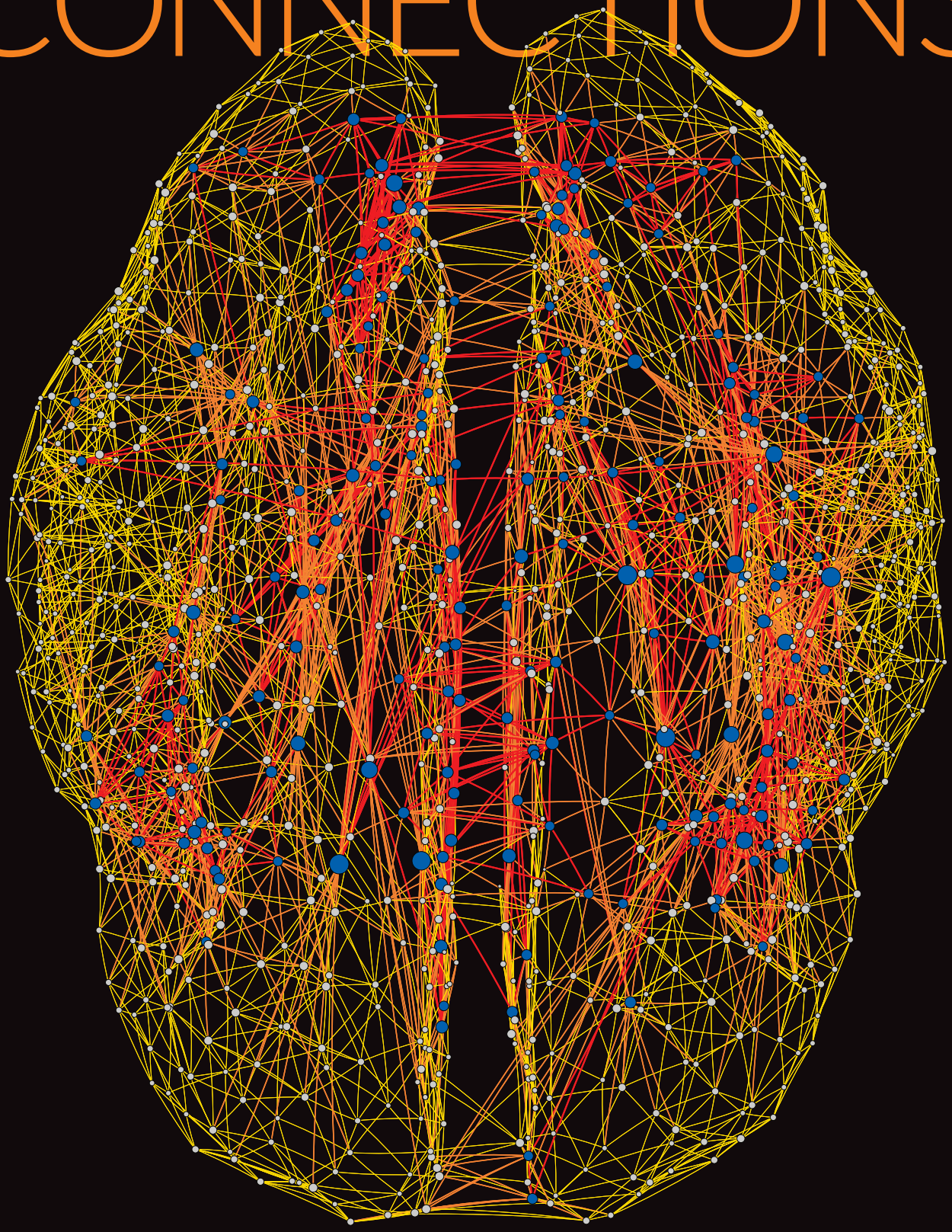
9. Disseminate knowledge and training
Accelerate progress by the rapid dissemination of newly developed skills and tools across the scientific and medical communities.

Explore more

- NIH BRAIN Initiative website: www.nih.gov/science/brain

BIG NEUROSCIENCE

CATALOGING THE CONNECTIONS



Viewing the brain as a network may help scientists tackle its complexity **By Tom Siegfried**

Mapping the human brain is a noble goal, but a rather ill-defined one. It's like making a map of the United States. You could just show political boundaries and the locations of cities. Or you might depict geographical features like mountains and rivers. Or transportation routes, like interstate highways and railroad tracks. You might even go Google Maps all the way and show the location of every individual house.

The brain possesses a similar diversity of scale: two hemispheres of convoluted gray matter, each with four regional lobes, traversed by superhighways of white matter fibers communicating with billions of individual cells. So some brain maps focus on outlining anatomical areas, others track the white matter wiring, still others divide the gray matter into tiny parcels and record their activity during different mental tasks. But eventually, scientists want to map everything. Their ultimate goal is a catalog of all the connections between all the brain's cells and regions, a master map known as the connectome.

It's a formidable task, comparable to identifying every building in the country and then tracing the routes of all the people and cars that travel among them. Yet mapping all those connections promises a huge potential payoff, many researchers say, and it will be essential to pursuing the even grander goals articulated by President Obama for understanding how the brain thinks and learns *(SN: 5/4/13, p. 22)*.

"The BRAIN Initiative of President Obama emphasizes determining connectivity," says neuroscientist Scott Emmons of Albert Einstein College of Medicine in New York. "And clearly we won't be able to understand the nervous system unless we know this connectivity."

Stanford University neuroscientist William Newsome, cochair of the National Institutes of Health panel establishing priorities for the president's project, agrees.

"This is what we interpreted the overarching goal of the BRAIN Initiative to be," says Newsome, "to map the circuits of the brain, measure the fluctuating patterns of electrical and chemical activity flowing within those circuits and to understand how their interplay creates our unique cognitive and behavioral capabilities."

Tough as that challenge seems, substantial progress has already been made. Scientists have completely described the connections in the primitive brain of the tiny roundworm *Caenorhabditis elegans*, for instance. Human studies have begun to map the white matter fibers that physically link various brain regions. Brain scans are revealing which regions operate in synchrony, a further clue to how they are connected.

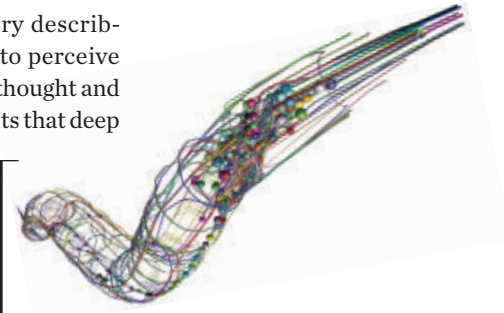
And using the mathematical theory describing networks, scientists have begun to perceive how brain cells cooperate to generate thought and behavior. In fact, network math suggests that deep insights into the brain's connections are possible even without mapping all the links for every single cell.

Ultimately such insights should assist in diagnosing and treating a number of brain diseases, such as schizophrenia, that result from faulty connections. "It's been suggested," says Emmons, "that some severe disorders such as schizophrenia and autism are in fact connectopathies."

A simple brain

In principle, the human connectome consists of literally every single link between every single nerve cell, or neuron, in the brain. But such a complete map is technologically out of reach at the moment. With a neuron population of roughly 85 billion, each maintaining thousands of connections, the connectome comprises an unfathomably vast network, with hundreds of trillions of links. So in humans, connectome research focuses on links between anatomical brain regions or just small parcels of brain tissue. The Human Connectome Project, launched by the National Institutes of Health in 2010, maps portions of gray matter on the cubic millimeter scale, roughly the size of a grain of salt. It's like mapping roads connecting cities and towns but ignoring side streets and individual houses.

An additional wrinkle of complexity distinguishes between physical links via white matter (cellular projections sheathed in myelin that wire regions together) and functional connections,



383

Number of neurons in a male *C. elegans*

85 billion

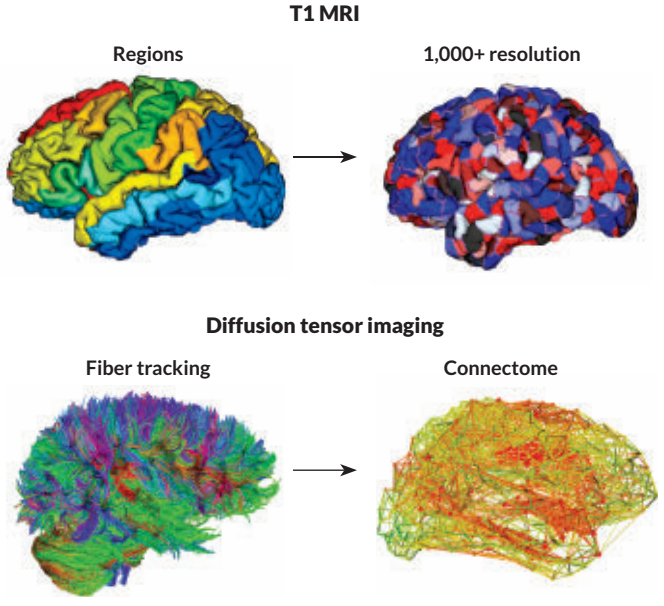
Number of neurons in a human brain

Using brain scanning technologies, scientists can create maps (opposite page) showing the brain's wiring, consisting of white matter fibers that link different parcels of the brain's gray matter. The most highly connected parcels, or hubs, are indicated by blue and white dots.

LEFT: COURTESY OF M.P. VAN DEN HEUVEL; RIGHT: COURTESY OF OPENWORM AND VIRTUAL WORM

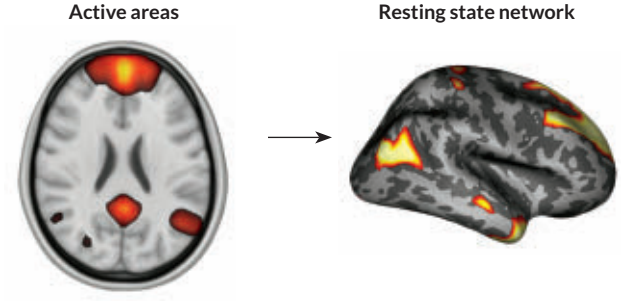
The structural connectome

T1 magnetic resonance scans identify the various anatomical regions of the brain and subdivide them into small parcels of gray matter tissue roughly equal in size (typically totaling more than 1,000 pieces). Another form of MRI, called diffusion tensor imaging, traces the paths of white matter fibers that connect the brain's various structural areas. The locations of the white matter fibers allow the construction of a connectome map that reveals how the parcels of gray matter are physically connected.



The functional connectome

Functional magnetic resonance imaging, or fMRI, records brain activity in different regions by measuring blood flow. Detecting parcels of brain tissue that are simultaneously active allows scientists to identify "resting state networks," functional modules of brain tissue involved in the performance of various tasks. By representing parcels of gray matter as nodes in a network, and white matter fibers as the links, scientists can apply graph theory (the mathematics of networks) to analyze how the structural and functional connectomes interact, thereby gaining insights into how the brain works as a whole.



identified by which brain regions are simultaneously active when performing a specific task.

This "functional connectome" is closely related to physical links, of course. But the human brain's complexity makes it infeasible to track that relationship on the scale of individual neurons. So scientists have sought some simpler substitutes to get insights into how neurons interact.

A favorite for this purpose is *Caenorhabditis elegans*, which possesses one of the simplest brains in the biosphere. A male *C. elegans* possesses 383 neurons (the hermaphrodite has even fewer), allowing scientists to catalog all the worm's neurons and trace their more than 2,000 connections using electron microscopy.

Worms and people share common ancestors, suggesting that the worm can provide information about how the human brain evolved. Although separated by eons of evolution, worms do use some of the same cellular messenger chemicals and display other properties recognizable in humans, Emmons pointed out in November at the annual meeting of the Society for Neuroscience. Both worm and human brain can be described, for example, by the mathematical theory of networks, officially known as graph theory. In graph theory, networks are represented by dots connected with lines; the lines are called links (or edges) and the dots are called nodes (or vertices). In *C. elegans*, the nodes are neurons, linked by the synapses through which the neurons communicate. Network math allows calculation of various properties, such as how many links a neuron makes on average to other neurons, and the minimum number of connections needed to transmit a signal from one neuron to any other one in the network.

Network analyses of *C. elegans* have revealed how sets of highly interconnected neurons can function as a module to govern a behavior such as mating. Using network math to discern the brain's modular organization might work in people as well as in worms, suggesting that connectome research may be useful even without mapping all the synapses, Emmons noted.

"Do we have to identify every single synapse to understand brain connectivity, or can we find computational subunits of neurons that do similar functions and treat them as a group?" he said at the neuroscience meeting. It may be possible, he believes, to show how networks are built from groups of neurons without the need to determine all the wiring within each group. "This is certainly a challenging and exciting goal as brain connectomics goes forward," Emmons said.

M.P. VAN DEN HEUVEL AND O. SPORNS/*J. OF NEUROSCIENCE* 2013

Neural hubs

One important finding is that worm brain connectomes are "small world networks," famous for how few steps it takes to link any two nodes *(SN: 2/17/07, p. 104)*. Such networks typically possess highly connected nodes, or hubs, that help shuffle signals from one node to another efficiently.

In the *C. elegans* hermaphrodite, 11 neurons have been identified as "rich club" hubs, neuroscientist Edward Bullmore of the University of Cambridge and collaborators reported last April in the *Journal of Neuroscience*. These hubs are not only well-connected in their own network, but are also connected to each other, forming a network, or club, of highly connected nodes.

Rich club nodes also exist in the human brain, even though the nodes are parcels of brain tissue rather than individual neurons. Similarly to social networks like Twitter, the brain's network consists of "communities" of anatomical regions that share information and participate in common tasks. Brain scans have identified several such communities, called resting state networks, that are related to important brain functions, such as vision, movement, hearing and touch. But the various resting state networks are not tightly connected to each other. So the brain needs a system to coordinate its various tasks and transmit information from region to region. That's where the rich club hubs enter the game.

In humans, rich club hubs are found in various brain regions, no matter their job. "Hubs tend to be present in all functional domains of the brain," says Martijn van den Heuvel of University Medical Center Utrecht in the Netherlands.

He and Olaf Sporns of Indiana University investigated the rich club hubs by mapping the white matter in 75 people. Out of 1,170 parcels of gray matter in each brain, on average 17 percent were highly connected enough to be considered rich club hubs. Such hubs were found in all 11 of the resting state networks examined in the study. Often those richly linked hubs showed up in "confluence zones" where resting state networks overlapped on the brain's surface layer.

Not only are the rich nodes highly connected within their network, they are also highly connected to each other — which is what makes them members of a club, van den Heuvel and Sporns found. "What we observe is that the level of connectivity between those hubs was around 40 percent higher than what we would expect," van den Heuvel said at the neuroscience meeting.

Their presence in all functional networks, along with their club membership, indicates that these rich club hubs anchor the brain's data sharing system, merging information from the various functional networks.

"In the brain or in neural systems, communication is not just sending a UPS package around with the content of the package remaining the same," van den Heuvel said. Data from different regions are always being combined and coordinated.

Thought and consciousness may involve a 'global workspace' in the brain that relies on rich club connections to manage communications.

Understanding the rich club will aid efforts to comprehend such high-level brain processes, van den Heuvel believes. Thought and consciousness, for instance, may involve a "global workspace" in the brain that relies on the network of rich club connections to manage communication among the brain's many regions.

"The global workspace does not coincide with a single anatomical or functional module in the brain, but rather involves a widely distributed neural system of long-distance anatomical projections," van den Heuvel and Sporns wrote last September in the *Journal of Neuroscience*.

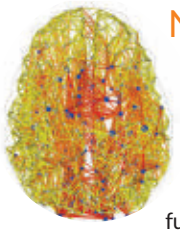
Brain as network

Already the network approach to understanding brain connections has led to insights about important mental functions such as learning and memory. One relevant finding is that the brain's networks are not static, but capable of rapid changes over time. And some networks are more flexible than others.

"Within the brains there are some regions that tend to be very rigid," says Danielle Bassett of University of Pennsylvania. "Core" regions involved in sensations and motions are typically rigid, she says, while peripheral systems, involved in thinking and making visual associations, tend to be more flexible.

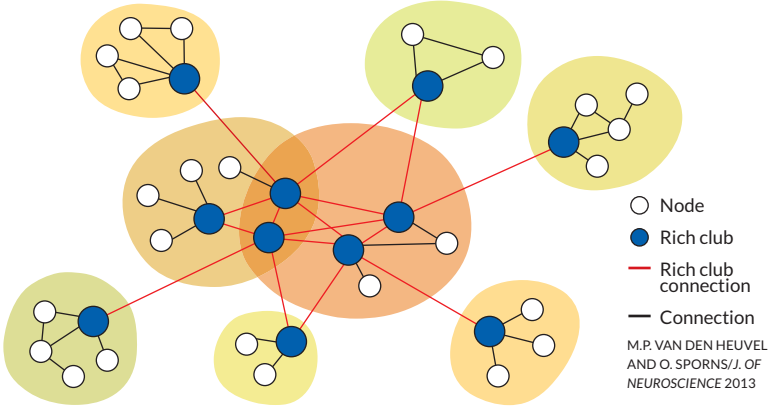
"People who have a more rigid core and more flexible periphery are those who learn better than individuals whose core is more flexible or whose periphery is more rigid," says Bassett. "So this separation of functions between core and periphery is actually quite important for how individuals learn."

Besides illuminating the workings of the normal



Network analysis

Within various brain regions, some parcels of gray matter (nodes, in network language) possess a substantially higher than average number of connections to other nodes. These highly linked nodes, or "hubs," are common in resting state networks (color shaded, below) associated with specific brain functions. Recent studies have shown that the hubs within a resting state network are also highly connected to hubs in other resting state networks (red lines). These "rich club" hubs (blue circles) probably play a major role, therefore, in merging the activity of various brain networks into the unified whole underlying consciousness.



M.P. VAN DEN HEUVEL AND O. SPORNS/*J. OF NEUROSCIENCE* 2013

brain, studies of network structure and function have also led to insights into brain disorders. Van den Heuvel points out that the central role of the rich club makes it a prime suspect in cases when the brain goes awry.

"If it's such a central system, one would suspect that abnormal wiring of the system might lead to brain dysfunction, and we indeed have some evidence that it is happening in schizophrenia and Alzheimer's," he says.

Some of that evidence comes from Bassett and collaborators. They have found numerous differences when comparing the brain networks of healthy individuals with those of schizophrenia patients. At the neuroscience meeting, Bassett outlined several findings from various groups over recent years. One major difference is in the strength of connections, measured by how likely linked nodes are to be simultaneously active, in schizophrenia versus healthy brains.

"Across practically every single area of the brain we see a decrease in strength in the schizophrenia networks as compared to those of controls. That suggests that there can be a very global decrease in communication constructs in schizophrenia," she said.

On the other hand, while connections are generally weaker, they are also more variable. In a healthy brain, highly connected hubs tend to have strong connections, less connected nodes have weaker connections. But in schizophrenia, a given hub will have some strong connections but also some weak ones, suggesting a lack of proper brain organization.

"Potentially we could interpret this as healthy controls are able to separate the functions that different brain regions have to perform well, while schizophrenics are not able to segregate those functions in the same way because their networks are disorganized," Bassett said.

Furthermore, it is in the brain's weaker connections where schizophrenia patients differ most from healthy people. Patterns of weak connections distinguish schizophrenic brains from healthy ones with 75 percent accuracy, Bassett and colleagues reported in 2012 in *NeuroImage*. And the weak connections differ in terms of their anatomical locations, often touching areas of the brain known to be involved in schizophrenia's symptoms. Measures of schizophrenia symptoms involving attention, memory and negative affect were all strongly related to networks of weak connections.

Similar network-based studies have begun to identify important features of ADHD and autism, other brain disorders believed to be related to faulty connections. In ADHD, connections are sparser than normal and medications appear to work by repairing the brain's network structure, Damien Fair, of Oregon Health & Science University in Portland, reported at the neuroscience meeting. In autism, on the other hand, nodes appear to be more connected than usual.

Understanding the connectome in all its complexity may not lead to immediate cures for brain diseases. But it's becoming clear that progress in fighting brain disorders, and understanding the normal brain, will not be possible without embracing graph theory — the mathematics of networks — for analyzing the brain's connections.

"In general the brain is indeed a network and we should approach it as such," says van den Heuvel. "And graph theory may be one of those techniques or tools to extract properties that might provide more information on how brain function can emerge from the underlying anatomy." ■

Explore more

- Human Connectome Project website: www.neuroscienceblueprint.nih.gov/connectome

Tom Siegfried is the former editor in chief of Science News.

FROM TOP: M.P. VAN DEN HEUVEL AND O. SPORNS/*J. OF NEUROSCIENCE* 2013; ADAPTED BY M. ATAROD

Breakthrough technology converts phone calls to captions.

New amplified phone lets you hear AND see the conversation.

The Captioning Telephone converts phone conversations to easy-to-read captions for individuals with hearing loss.

Do you get discouraged when you hear your telephone ring? Do you avoid using your phone because hearing difficulties make it hard to understand the person on the other end of the line? For many Americans the telephone conversation – once an important part of everyday life – has become a thing of the past. Because they can't understand what is said to them on the phone, they're often cut off from friends, family, doctors and caregivers. Now, thanks to innovative technology there is finally a better way.

A simple idea… made possible with sophisticated technology. If you have trouble understanding a call, the Captioning Telephone can change your life. During a phone call the words spoken to you appear on the phone's screen – similar to closed captioning on TV. So when you make or receive a call, the words spoken to you are not only amplified by the phone, but scroll across the phone so you can listen while reading everything that's said to you. Each call is routed through a call center, where computer technology – aided by a live representative – generates immediate voice-to-text translations. The captioning is real-time, accurate and readable. Your conversation is private and the captioning service doesn't cost you a penny. Captioned Telephone Service (CTS) is regulated and funded by the Federal Communications Commission (FCC) and is designed exclusively for individuals with hearing loss. In order to use CTS in your home, you must have standard telephone service and high-speed Internet connectivity where the phone will be used. Federal law prohibits anyone but registered users with hearing loss from using IP Captioned Telephones with the captions turned on. Callers do not need special equipment or a captioning phone in order to speak with you.

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SCREENTIME

Lend an ear to science

Pop music hit maker Clive Davis knows a catchy song when he hears one. Now an app aims to define that elusive quality more concretely. Designed by computer and cognitive scientists at the University of Amsterdam and Utrecht University in the Netherlands, Hooked! asks citizen scientists to help uncover the mystery ingredients of a hook — the most memorable part of a song. The results might illuminate how music taps into memories and emotions in the brain. First the app drops the needle somewhere in the middle of one of the 2,000 most popular songs of all time. Listeners quickly report whether they know the tune or not. To test whether the listener really does know the song, the app then turns off the music. Listeners follow along in their heads until the tune restarts, then judge whether the song is in the right place or not. The better people are at remembering the song, the more likely the snippet is to be a hook, the researchers reason. Occasionally, the app also asks people to pick the catchiest snippet of a song. As people tune in, the program will analyze which sound patterns and qualities make a hook memorable. Hooked! is available free for iOS devices in the iTunes store. — *Laura Sanders*

Beautiful Geometry
Eli Maor and Eugen Jost
Graphic illustrations serve as both beautiful abstract art and helpful explanations in this overview of geometric theorems and patterns. *Princeton Univ., $27.95*

The Book of Black
Clifford A. Pickover
From black holes to the Black Death, many of the topics covered in this clever compendium of dark things include interesting scientific explanations. *Dover, $25*

The Perfect Theory
Pedro G. Ferreira
An astrophysicist explains Einstein's theory of general relativity and lays out the scientific battles that it has spawned. *Houghton Mifflin Harcourt, $28*

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BOOKSHELF

The Sixth Extinction

An Unnatural History

Elizabeth Kolbert

Almost nothing in nature is so rare as a mass extinction. On only five occasions in Earth's long history has a large fraction of the planet's biodiversity disappeared in a geological instant. But, journalist Kolbert reminds us in her new book, we are well on our way to making it six.

A lesser writer tackling this subject might offer up a dreary list of dead and dying species; Kolbert instead tells a scientific thriller. The tale begins in 1739, when strange bones turned up near the Ohio River. Stumped, the French scientist Georges Cuvier declared they must belong to a mammal that no longer exists, which he called the mastodon. As evidence for such archaic forms piled up, Cuvier went further, proposing that Earth's history is full of lost species, and sometimes they wink out in large numbers.

Not until the last few decades did paleontologists fully accept this "catastrophism." Most scientists now believe a meteor impact did in the dinosaurs, as well as the ammonites, extinct mollusks to which Kolbert devotes a loving chapter. That meteor had nothing on the earlier Permian extinction, though, which nearly wiped out multicellular life.

Humans are the new catastrophe. Large mammals are now mostly gone or headed that way, and we are pushing out other biota through habitat destruction and species introductions, Kolbert writes. Ecologists are feverishly studying these phenomena; Kolbert follows them to fragmented tropical rainforests in Panama and Peru, caves of bats stricken with white-nose syndrome in New York and acidifying coral islands on Australia's Great Barrier Reef. These modern eco-disasters are depressingly familiar, but united by Kolbert's masterful reporting, they gain a new urgency.

The scientists Kolbert meets also offer a glimmer of hope. We are, if perhaps a singularly destructive species, also unique in systematically gathering and preserving knowledge about our world. The big question, which Kolbert leaves open, is whether we can use this knowledge to avoid dooming much of the rest of life on Earth — and with it, possibly ourselves. — *Gabriel Popkin*
Henry Holt, $28

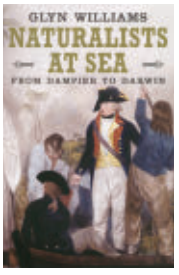
S-DMIT/ISTOCKPHOTO

BOOKSHELF

Naturalists at Sea

From Dampier to Darwin

Glyn Williams



For centuries after Columbus, the flora and fauna of the New World remained a mystery to Europeans. But in the 1600s and 1700s, explorers began to visit and describe what were then considered remote corners of the Earth. Williams brings to life these naturalists who preceded Charles Darwin. While others on the ships mapped the blank spots on their charts, the naturalists scrambled onshore and combed the waters to catalog all that lived.

The book meanders much as they did. Williams, a historian, starts with self-taught Englishman William Dampier, who hopped a ship to Java at age 20 to begin a 13-year trip around the world. Dampier's notes and drawings awoke European scientists in the late 1600s to species in Australia and many other exotic locales.

In 1767, French naturalist Philibert de Commerson set out on a six-year tour that took him to South America, Java and Madagascar. He shipped home 34 cases of plants, seeds, fish and drawings — some 3,000 species new to Europeans. James Cook's first Pacific voyage collected such a flood of species that the naturalists on board ran out of storage and began pressing plants between the pages of Milton's *Paradise Lost*. After Cook had mapped New Zealand and part of Australia, the retinue returned home with reports of an unknown people, Aborigines, and one of their words: kangaroo.

The book's details are the best part. We learn that Dampier was in reality a buccaneer who raided Spanish ships and cataloged plants and animals on the side. Commerson's ship took two months just to get through the Straits of Magellan. And Commerson's assistant Jean Baret was revealed, after having crossed the South Pacific with the crew, to be a woman, Jeanne Baret. After Commerson died in 1773 on Mauritius, Baret married and sailed back to France, becoming the first woman to circumnavigate the globe.

Many of these naturalists never gained recognition while alive. Some of German scholar Georg Wilhelm Steller's notes survived, but he died in Siberia. The Bering Strait, named for his ship captain, is better known than tiny Steller's Island. Alejandro Malaspina, whose ships sent 16,000 plant specimens to Spain, ended up in prison. Upon his release, he had to sell the sextant that had guided him around the Pacific.

It's quite a journey. While these naturalists exist in Darwin's shadow today, their work lives on through their writings and their specimens, seminal contributions to the unveiling of a new world. — *Nathan Seppa*
Yale Univ., $29.95

JANUARY 11, 2014

Long and short of it

Big number names depend on where you live. The short scale is used in most English-speaking countries, while the long scale is common in Europe.

Short scale		Long scale
billion	10^9	milliard
trillion	10^{12}	billion
quadrillion	10^{15}	billiard
quintillion	10^{18}	trillion
sextillion	10^{21}	trilliard
septillion	10^{24}	quadrillion
octillion	10^{27}	quadrilliard
nonillion	10^{30}	quintillion
decillion	10^{33}	quintilliard
undecillion	10^{36}	sextillion
duodecillion	10^{39}	sextilliard
tredecillion	10^{42}	septillion

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Microbiome musings

The January 11, 2014, issue of Science News *focused on the microbiome, the diverse collection of microbes that reside in and on humans and other organisms.*

Mark Bach looks forward to seeing what scientists can learn from the study of these tiny hitchhikers. "As our understanding of the microbial world — or more correctly, the world that we share with microbes — expands, we need to be ready to accept the unexpected," he wrote in an e-mail. "Surprises await us all!" Online commenter **Steve Foster** called "Microscopic menagerie" (*SN: 1/11/14, p. 14*) "fascinating" and suggested additional reading: "Perhaps readers would also enjoy rereading Lynn Margulis' *Symbiotic Planet*; such a review would help provide context to such newer reports as this one."

Tina Hesman Saey's story about testing her own microbiome inspired a change of heart in **Mark Mailloux**. "I read your magazine from cover to cover," he e-mailed, "but I confess that I am much more interested in physics and astronomy than biology topics. I often get MEGO syndrome (My Eyes Glaze Over) in biology articles — until I came across "Me and my microbiome" (*SN: 1/11/14, p. 28*). All of a sudden it became real. Results from an actual person (not a labful of genetically weird rats) captured my attention. I look forward to updates from her as results come in from these studies trying to find out what 'normal' is and how she fits in."

The number name game

In "The vast virome" (SN: 1/11/14, p. 18), ***Tina Hesman Saey*** *noted that humans share the planet with 10 quintillion, or 10^{30}, virus particles.*

Reader **ms** questioned this figure on the *SN* website. "In America, a quintillion is 10^{18}, not 10^{30} as it is in Britain. So, when you claim that there are 10 quintillion virus particles on our planet, and then say the number is 1 followed by 31 zeroes, is that because you've incorrectly converted an American quintillion with the British definition?"

Saey explains: "The reader is correct that we meant nonillion, not quintillion. There are two systems for naming big numbers: the short scale and the long scale. The long scale was invented in the late 15th century in France and gives a new name to every number one million times bigger than the previous number. So one million million is a billion (10^{12}), a million billion is a trillion (10^{18}) and so on (see table, left). The long scale is used in Europe and Latin America, but no longer in the United Kingdom — though it is still often called the British system.

French mathematicians in the 17th century decided to assign names to every number one thousand times greater than the last, so a billion is 1,000 million or 10^9, and a trillion is 1,000 billion (10^{12}). This short scale is the convention in the United States. The United Kingdom switched to the short scale in 1974, although France had reverted back to the long scale in 1948. *Science News*, published in the United States, should have said 10 nonillion viruslike particles."

Lamarckism not quite revived

Laura Sanders *described mice passing on the fear of a smell to their offspring in "Fear can be inherited" (SN: 1/11/14, p. 13).*

"Isn't that Lamarckian evolution?" e-mailed **Paul Hyer**. Not exactly, **Sanders** says. "In the early 1800s, before genes were found to carry heritable information, French naturalist Jean-Baptiste Lamarck argued that environmental influences can shape an animal and its descendants in specific ways.

Epigenetics, in which the environment changes gene behavior without altering the genes themselves, has given a glimmer of hope to die-hard Lamarckians. Epigenetics does allow traits acquired during an organism's lifetime to be passed on to offspring. Because epigenetic changes can affect many aspects of an organism, the process boosts genetic variation overall, but does not promote specific changes as Lamarck might have argued. Those variations then become fodder for natural selection to act on."

"How I BEAT My Acid-Reflux Nightmare!"

"Now, I can eat even the spiciest foods without worry!"

By Ralph Burns;
"Former" acid reflux sufferer

Here's My Story: I've Suffered With Acid Reflux for Almost 40 Years Now. Unless you experience it, you can't imagine how horrible it is. Every time I ate spicy foods I would get what I called **"ROT GUT"**. Like something was rotting in my stomach. But now I can eat anything... No matter how spicy. Even if I never could before.

Let me explain…

For the better part of my life, I purposely avoided a lot of foods. Especially ones with even a tiny bit of seasoning. Because if I didn't, I'd experience a burning sensation through my esophagus— like somebody poured hot lead or battery acid down my throat. Add to that, those disgusting "mini-throw ups" and I was in "indigestion hell".

Doctors put me on all sorts of antacid remedies. But nothing worked. Or if they did, it would only be for a brief period. And then boom! My nightmare would return.

Sometimes, I felt like I was dying. The pain was unbearable and nothing could make it stop.

But then my wife, who occasionally suffered with the same problem; gave me one of her prescription acid blockers. It was a miracle. I felt like I could live again. Because before that, I was just miserable. I wanted to kill myself. But thankfully, it worked, and worked well.

"I was beside myself. What was I gonna do? Keep taking the pills, or suffer with problems that could ultimately be my demise".

I felt great, until about one year ago; when I read an FDA warning that scared the heck out of me. It went something like this…

FDA WARNING! Using proton pump inhibitors (PPIs) on a long term basis, increases your risk of hip, bone and spinal fractures.

That's a particular concern to me, since many acid blockers are PPI's. I've gone through two back surgeries and bilateral hip replacements. I had to ask myself, could PPI's have been responsible for my medical woes? After all...

"The Recommended Treatment for Prilosec®, Prevacid® and Other PPI's is Only 14-DAYS, I Took Them for 14 YEARS!"

I was "between a rock and a hard place". Stop using the PPIs and I'm a "dead man in the water". It would be unbearable. I wouldn't be able to eat anything. I'd have to go on a water diet.

But that FDA warning was scary. I knew I had to stop or else risk developing spinal stenosis. My mother had that. And I watched her die a horrible death. Her spine just fractured. It was the worst death. She didn't deserve that. And neither do I.

I had to quit. So I stopped taking PPI's for a day or so. But my indigestion was worse than ever. I would rather take the chance of a spinal fracture than to live like that again. I tried everything. Even started using home remedies like apple cider vinegar. But it just felt like I was pouring even more acid down my throat. **Then one day at dinner,** a friend of mine said "why don't you try an aloe drink?" I said 'aloe drink'? Jeez. That doesn't sound good at all!" The next day he brought me a case of something called *AloeCure*®. I was skeptical, but I was desperate! So instead of being an ingrate I decided to try it.

And here's the best part. The next day we had Italian food — my worst enemy. But for the first time in 40 years I didn't get indigestion without relying on prescription or OTC pills and tablets. Finally, I just didn't need them anymore!

I was so thrilled; I wrote the *AloeCure*® company to tell them how amazing their product is. They thanked me, and asked me to tell my story... The story that changed my life. I said "Sure, but only if you send me a hefty supply of *AloeCure*®. I just can't live without it."

63 year old Ralph Burns enjoying a spicy-hot portion of Lobster Fra Diavolo. Just 15 minutes after taking *AloeCure*®

"Every time I ate something that didn't agree with me… I'd get what I called 'Rot Gut' — like my stomach was rotting out!"

But don't believe me. You have to try this stuff for yourself. I recommend *AloeCure*® to anyone who suffers with the same problem I did. It gives you immediate relief. You'll be grateful you did. I sure am. It's the best thing that's happened to me in a long, long time.

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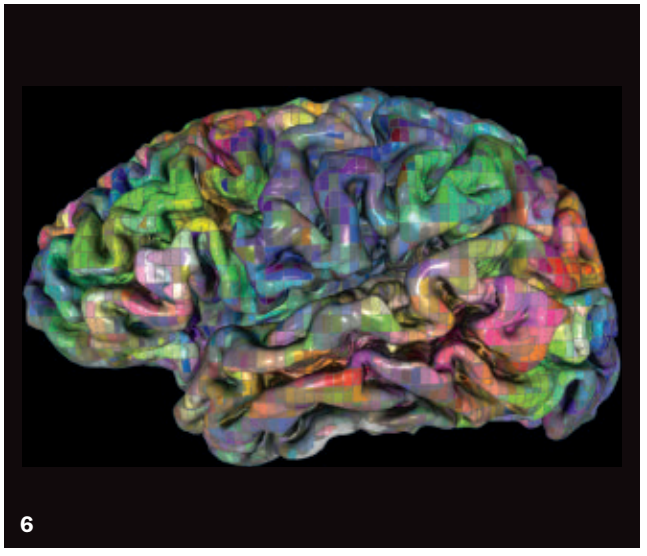
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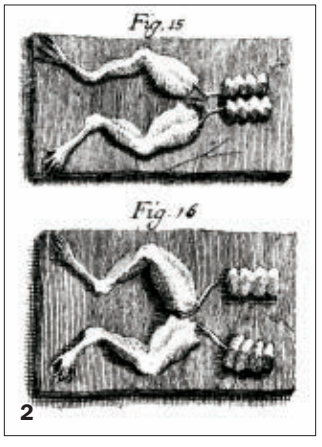

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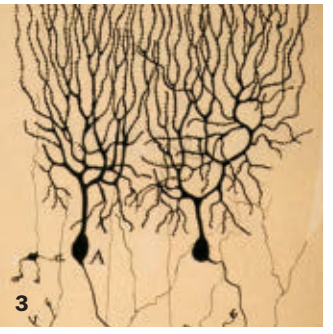
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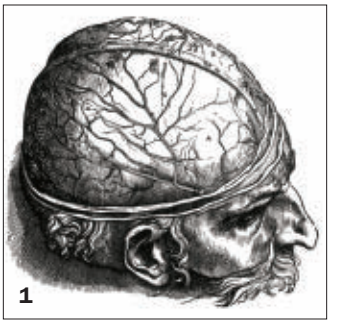
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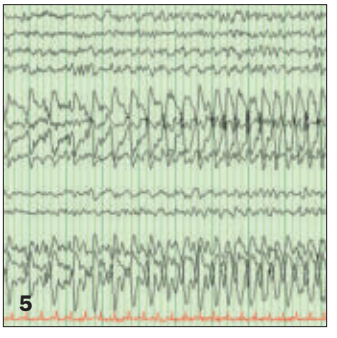
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Ways of seeing the brain inspire notions of how it works

The mysterious contents of the skull have long captivated their owners. Ancient Egyptians treated brain injuries by pouring milk in both ears. Aristotle believed the brain was a cooling unit for the heart. Galen, the leading physician of the Roman Empire, claimed that "animal spirits" imbued the brain with its abilities. These ideas were a product of limited tools and unscientific preconceptions. As scientists have developed more sophisticated methods and ideas, their understanding of how the brain works has shifted too.
— Laura Sanders

1. Anatomy lesson
In the 1500s, Flemish anatomist Andreas Vesalius began studying the anatomy of corpses. His detailed, lifelike representations, many published in 1543 in *De Humani Corporis Fabrica*, led scientists to question some antiquated ideas about how the human brain works and what makes it unique. Vesalius was skeptical of the notion that nerves are conduits for "animal spirits," and showed that people have fluid-filled ventricles proportionate in size to those of animals. Earlier thinkers had proposed that outsized ventricles gave human brains their exceptional power.

2. Jolt of inspiration
In experiments during the 1780s that inspired Mary Shelley's 1818 novel *Frankenstein*, Luigi Galvani hooked up a long metal wire to recently deceased frogs during a lightning storm and watched as each strike caused the frogs' legs to twitch. Electricity was the mysterious "animal spirit" that carried the impulse for muscle contraction, Galvani concluded. His results gave birth to the field of neurophysiology, in which scientists study nerve cells' electrical communication.

3. Neurons in black and white
Aided by a black stain that could highlight individual neurons and a masterful drawing hand, the Spanish researcher Santiago Ramón y Cajal ushered in modern neuroscience in the late 1800s. His exquisite renderings of complex and diverse neurons showed that instead of being a tangled nest of fused fibers, the nervous system is an intricately connected network of discrete nerve cells, a claim called the neuron doctrine. From his drawings, Cajal correctly guessed that nerve impulses travel directionally along cellular tendrils to send messages to adjacent cells.

4. Form to function
Over the years, rare brain injuries have offered scientists a way to link specific cognitive powers to certain brain regions. After a tamping iron blasted through the front part of his brain (shown) in 1848, the mild-mannered rail worker Phineas Gage turned nasty. His dramatic change in character told scientists that the damaged part of the brain was important for personality. Other famous cases, such as the patient of 19th century French physician Pierre Paul Broca who was unable to speak any word other than "tan," and the 20th century patient known by the initials H.M., who lost his memory after a surgery, also provided rare glimpses into the geography of brain function.

5. Electrical traces
Since Galvani's jumping frogs, scientists have made leaps in understanding electrical signals in the brain. In the late 1950s, electrodes recorded single neurons in anesthetized animals as they responded to particular visual inputs. Later, scientists were able to record electrical activity from awake animals. Electrical activity ensconced in a skull is now detectable by electrodes placed on the head using a method called electroencephalography, or EEG (shown).

6. The brain at work
Toward the end of the 20th century, researchers finally developed methods that allowed them to visualize brain activity as it happened. In the 1970s, researchers developed the first positron emission tomography scanner, a machine that could track molecular activity in the brain using radioactive probes. Scientists later began to use magnetic resonance imaging, or MRI (shown), to produce detailed images of the brain's anatomy, connections and behavior. The technology has produced insights into how different parts of the brain work together to produce thoughts, memories, emotions and other mental experiences.

1, 2. THE GRANGER COLLECTION, NYC; 3. INSTITUTO CAJAL/WIKIMEDIA COMMONS; 4. JOHN DARRELL VAN HORN/UCLA LABORATORY OF NEURO IMAGING, 2012; 5. M. JAVIDAN/ *EPILEPSY RESEARCH AND TREATMENT* 2012; 6. ALEX HUTH, JAMES GAO AND JACK GALLANT/UC BERKELEY

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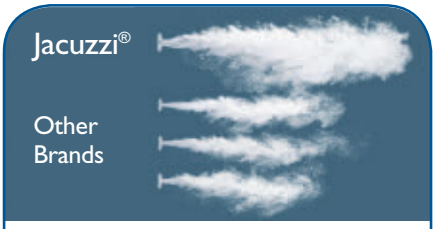

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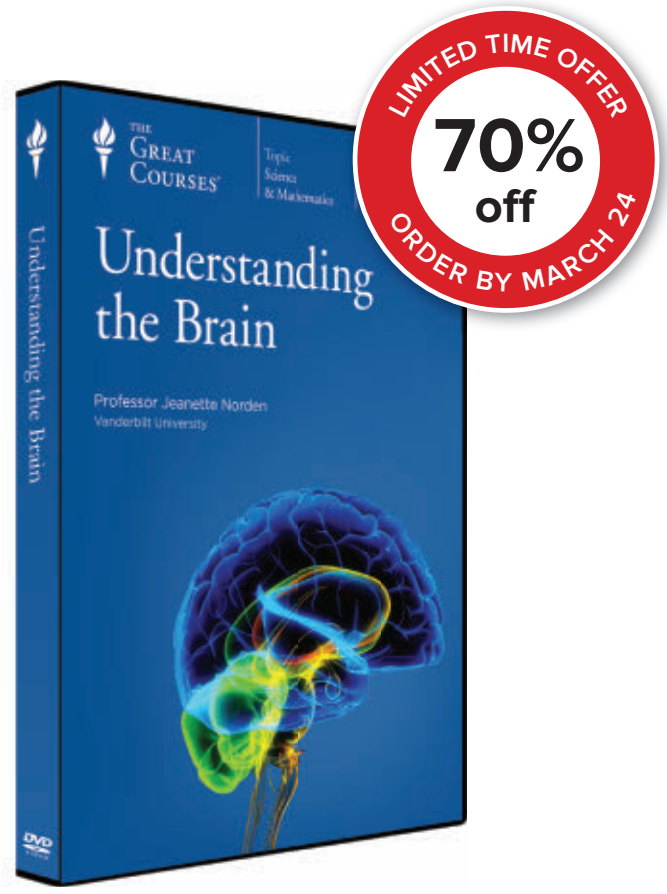

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