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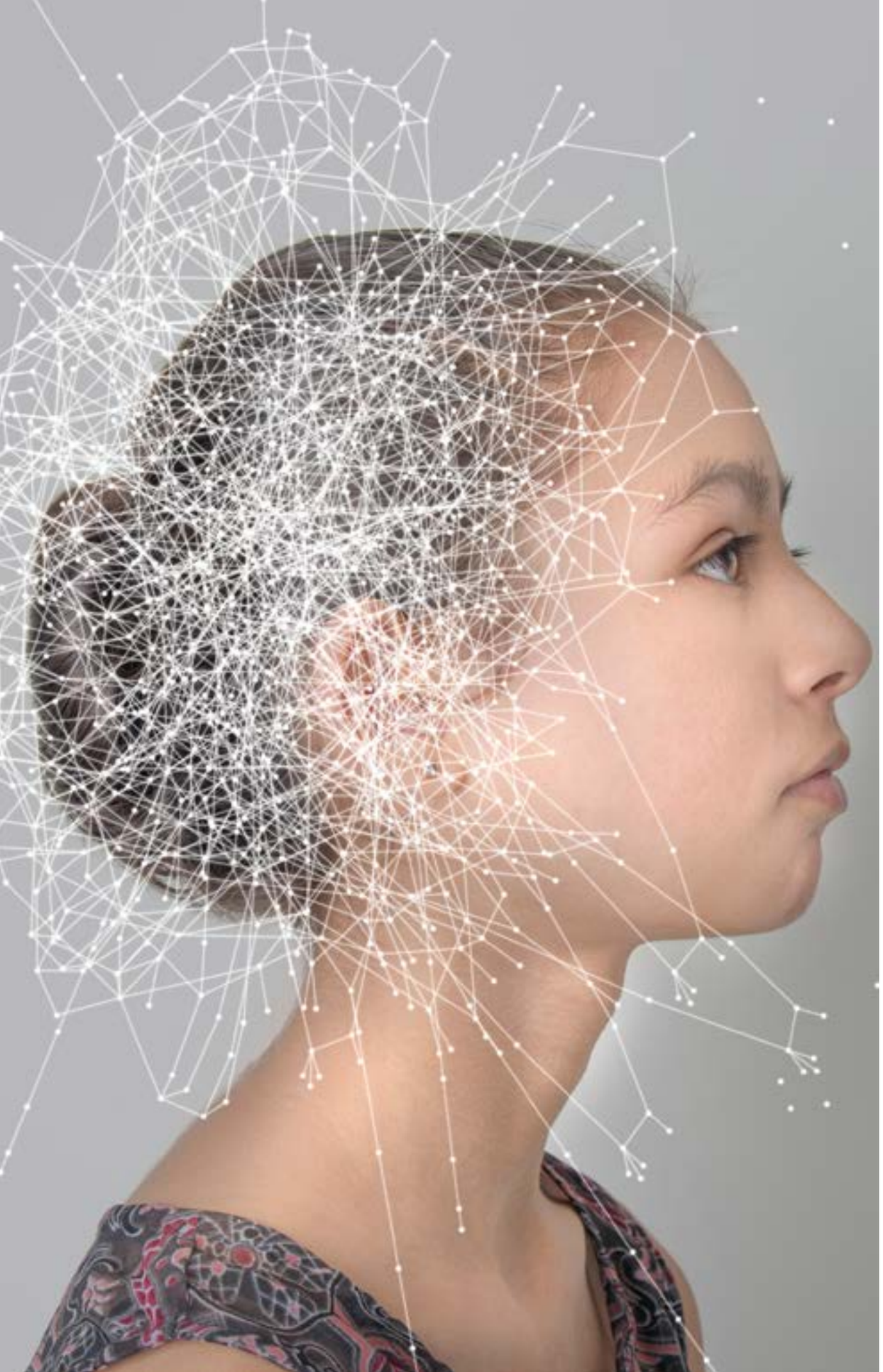
SPECIAL REPORT

The Science of Memory

Exciting findings about the mind's most intriguing faculty

INCLUDING

- How we remember the future
- Devices that prevent forgetfulness
- Portraits of memories



FROM THE EDITOR

Total Recall

Last year memory researchers John Wixted and Laura Mickes wrote on ScientificAmerican.com that while eyewitness testimony is widely considered unreliable evidence (eyewitness misidentifications have been shown to be involved in a whopping 70 percent of 349 wrongful convictions), we shouldn't throw the baby out with the bathwater. Eyewitness testimony collected under certain circumstances could still be invaluable. The trick about memory is that sometimes it's reliable and other times it's not. Memory is malleable.

Remarkably, discovery has only slowly progressed about how memories form in the brain, why certain memories are stored over others, and what preserves the integrity of those individual memories. In this issue's special report, we've included the latest findings on the tools researchers have devised to get at these questions. As Helen Shen describes in "Portrait of a Memory," scientists are refining their techniques to decode discrete memories with increasing precision, producing "engrams," images of brain activity. Investigators Matthias Kliegel and Nicola Ballhausen explain in "Foresee and Forget: How to Remember the Future," a fascinating area of research on "prospective" memory—that is, memory used to recall things that need to be done in the future—a vital skill for planning your day's activities. And Dana G. Smith reports in "Brain 'Pacemaker' Could Help You Remember Only What You Might Forget," on a new technology that might stimulate the brain to summon up something it seems to have forgotten, in case your prospective memory is lagging on that particular day.

As always, enjoy and let us know what you think!

Andrea Gawrylewski

Collections Editor: editors@sciam.com

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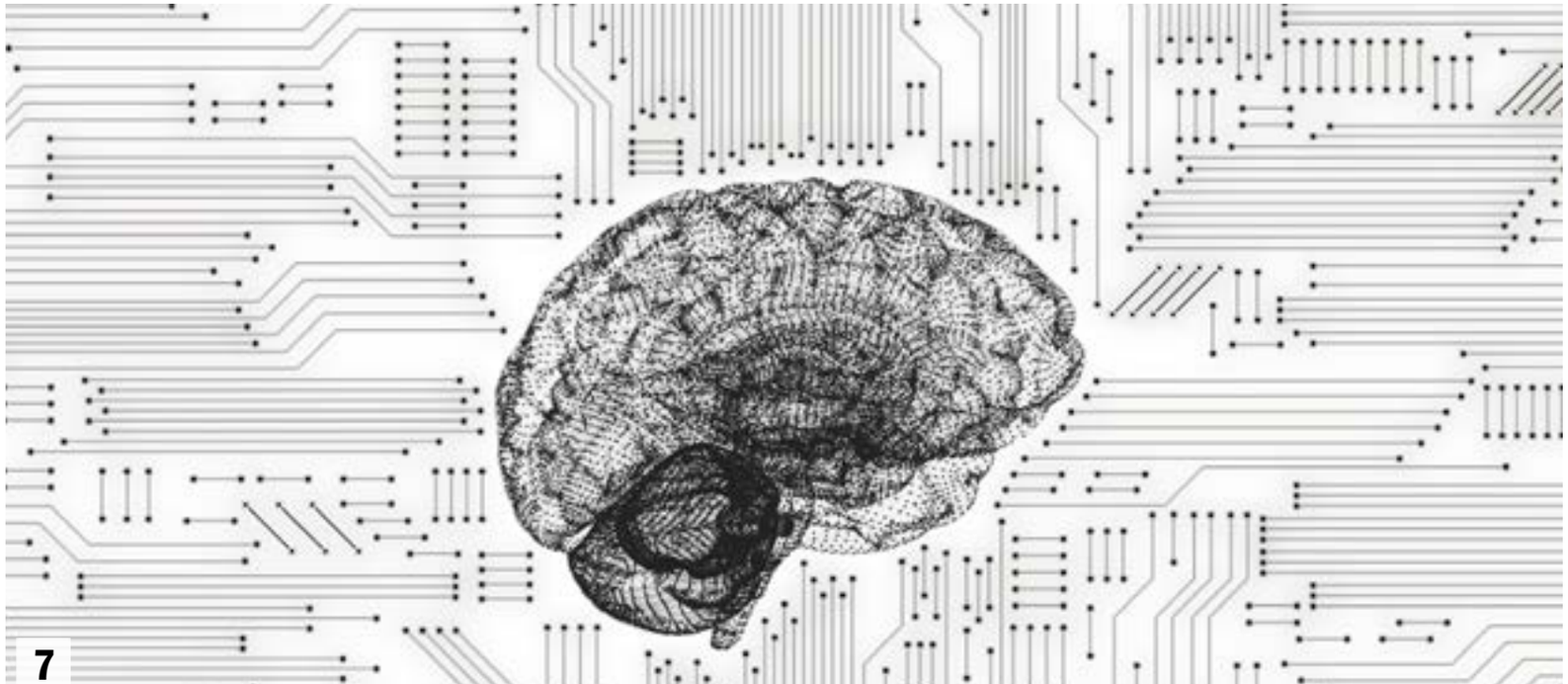

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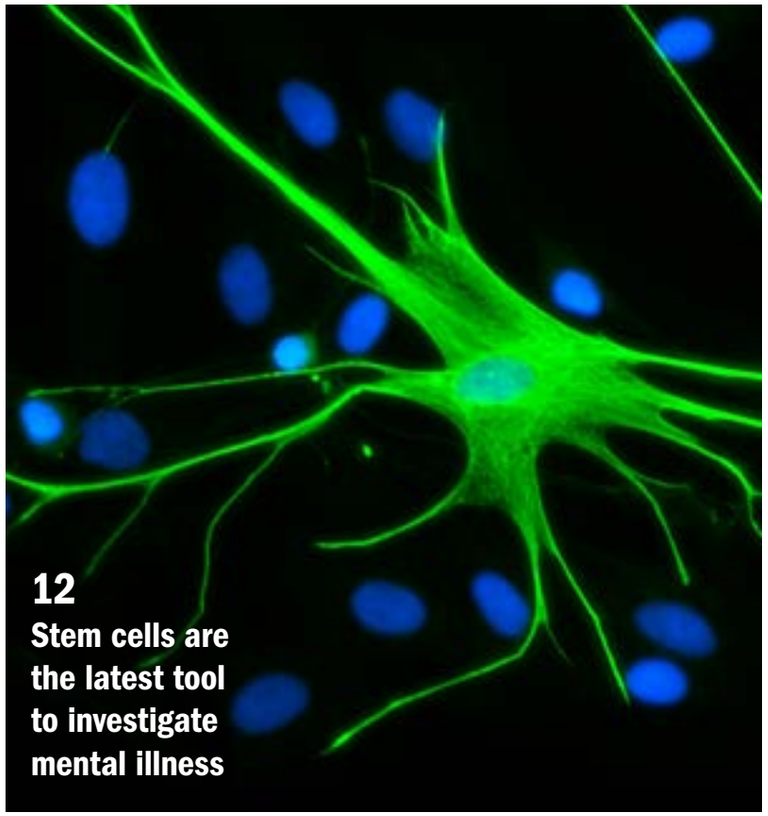

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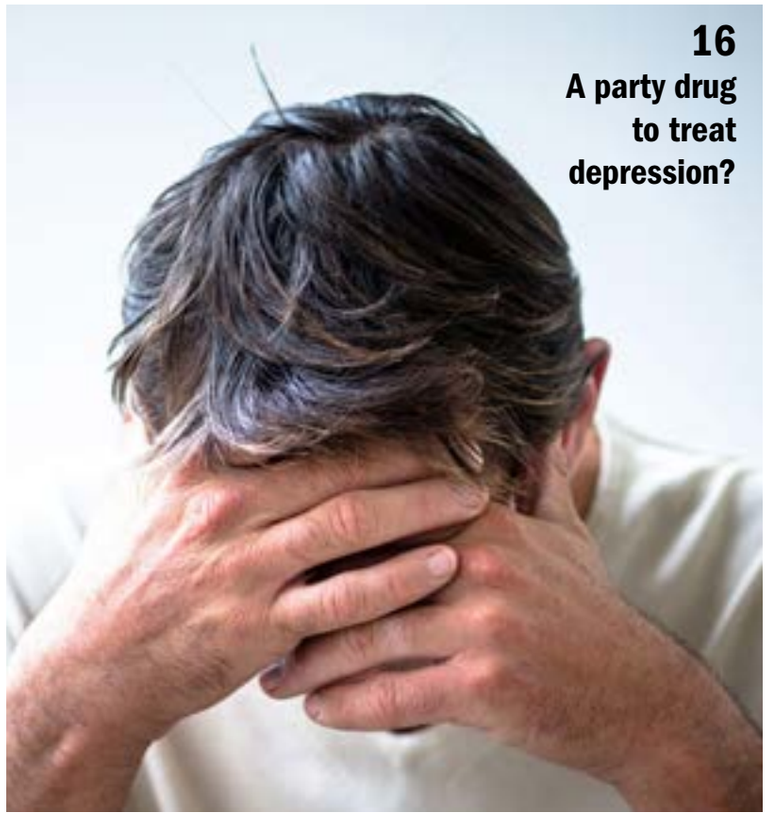

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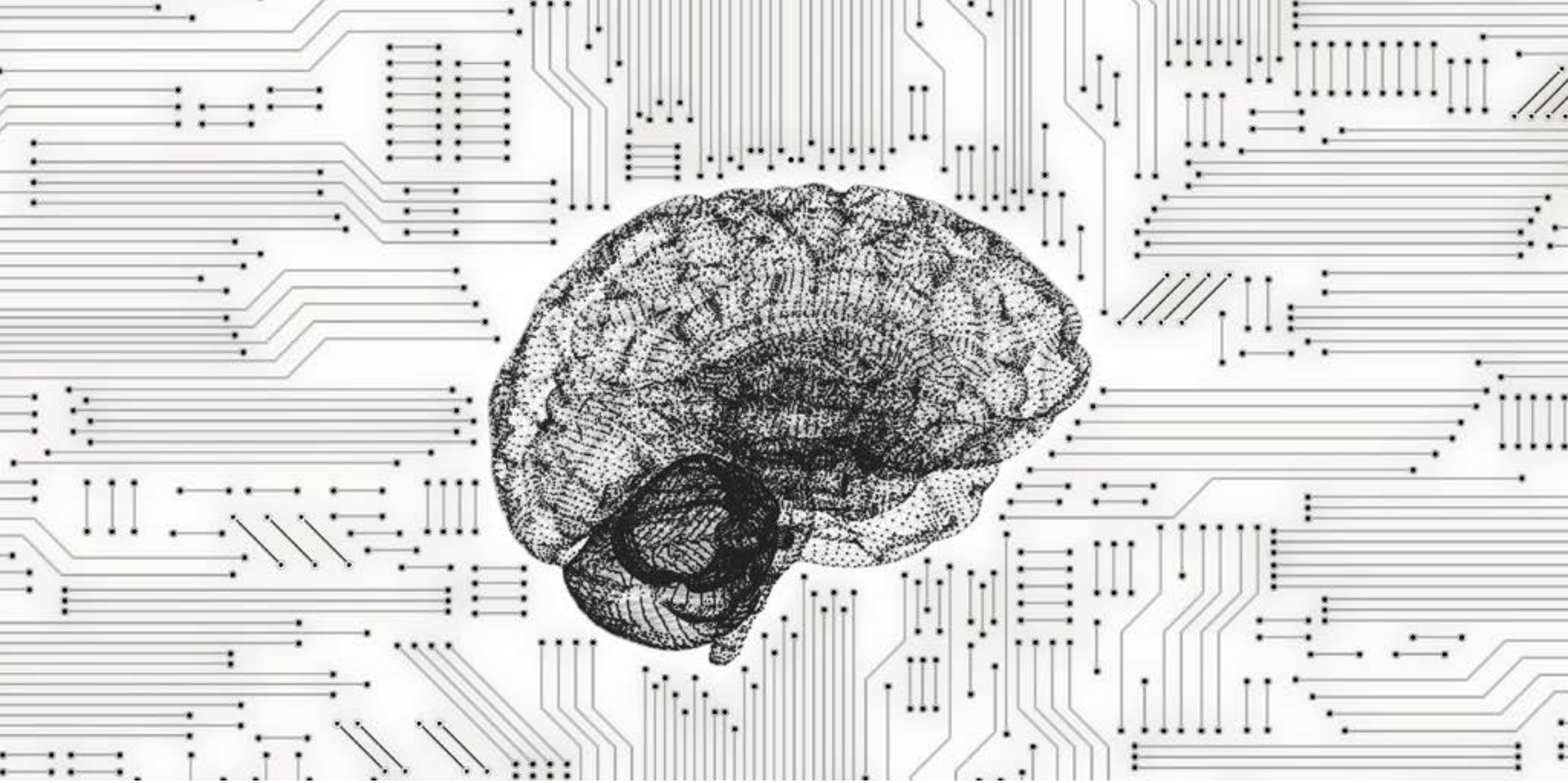

NEWS

Brain Implants for Mood Disorders Tested in People

AI-controlled devices record neural activity and automatically stimulate the brain

WIGGLESTICK *GETTY IMAGES*

Brain implants that deliver electrical pulses tuned to a person's feelings and behavior are being tested in people for the first time. Two teams funded by the U.S. military's research arm, the Defense Advanced Research Projects Agency (DARPA), have begun preliminary trials of closed-loop brain implants that use algorithms to detect patterns associated with mood disorders. These devices can shock the brain back to a healthy state without input from a physician.

The work, presented last November at the Society for Neuroscience (SfN) meeting in Washington, D.C., could eventually provide a way to treat severe mental illnesses that resist current therapies. It also raises thorny ethical concerns, not least because the technique could give researchers a degree of access to a person's inner feelings in real time.

The general approach—using a brain implant to deliver electric pulses that alter neural activity—is known as deep-brain stimulation. It is used to treat movement disorders such as Parkinson's disease, but has been less successful when tested against mood disorders. Early evidence suggested that constant stimulation of certain brain regions could ease chronic depression, but a major study involving 90 people with depression found no improvement after a year of treatment.

The scientists behind the DARPA-funded projects say that their work might succeed where earlier attempts failed, because they have designed their brain implants specifically to treat mental illness—and to switch on only when needed. "We've learned a lot about the limitations of our current technology," says Edward Chang, a neuroscientist at the University of California, San Francisco, who is leading one of the projects.

DARPA is supporting Chang's group and another at Massachusetts General Hospital (MGH), with the eventual goal of treating soldiers and veterans who have depression and post-traumatic stress disorder. Each team hopes to create a system of implanted electrodes to track activity across the brain as they stimulate the organ.

The groups are developing their technologies in experiments with people with epilepsy who already have electrodes implanted in their brains to track their seizures. The researchers can use these electrodes to record what happens as they stimulate the brain intermittently—rather than constantly, as with older implants.

Mood Map

At the SfN meeting, electrical engineer Omid Sani of the University of Southern California—who is working with Chang's team—showed the first map of how mood is encoded in the brain over time. He and his colleagues worked with six people with epilepsy who had implanted electrodes, tracking their brain activity and moods in detail over the course of one to three weeks. By comparing the two types of information, the researchers could create an algorithm to decode that person's changing moods from their brain activity. Some broad patterns emerged, particularly in brain areas that have previously been associated with mood.

Chang and his team are ready to test their new single closed-loop system in a person as soon as they find an appropriate volunteer, Sani says. Chang adds that the group has already tested some closed-loop stimulation in people, but he declined to provide details because the work is preliminary.

The MGH team is taking a different approach. Rather than detecting a particular mood or mental illness, they want to map

the brain activity associated with behaviors that are present in multiple disorders—such as difficulties with concentration and empathy. At the SfN meeting, they reported on tests of algorithms they developed to stimulate the brain when a person is distracted from a set task, such as matching images of numbers or identifying emotions on faces.

The researchers found that delivering electric pulses to areas of the brain involved in decision making and emotion significantly improved the performance of test participants. The team also mapped the brain activity that occurred when a person began failing or slowing at a set task because they were forgetful or distracted, and found they were able to reverse it with stimulation. They are now beginning to test algorithms that use specific patterns of brain activity as a trigger to automatically stimulate the brain.

Personalized Treatment

Wayne Goodman, a psychiatrist at Baylor College of Medicine, hopes that closed-loop stimulation will prove a better long-term treatment for mood disorders than previous attempts at deep-brain stimulation—partly because the latest generation of algorithms is more personalized and based on physiological signals, rather than a doctor's judgment. "You have to do a lot of tuning to get it right," says Goodman, who is about to launch a small trial of closed-loop stimulation to treat obsessive-compulsive disorder.

> "You have to do a lot of tuning to get it right."
> —Wayne Goodman

One challenge with stimulating areas of the brain associated with mood, he says, is the possibility of overcorrecting emotions to create extreme happiness that overwhelms all other feelings. Other ethical considerations arise from the fact that the algorithms used in closed-loop stimulation can tell the researchers about the person's mood, beyond what may be visible from behavior or facial expressions. While researchers won't be able to read people's minds, "we will have access to activity that encodes their feelings," says Alik Widge, a neuroengineer and psychiatrist at Harvard University, and engineering director of the MGH team. Like Chang's and Goodman's teams, Widge's group is working with neuroethicists to address the complex ethical concerns surrounding its work.

Still, Chang says, the stimulation technologies that his team and others are developing are only a first step toward better treatment for mood disorders. He predicts that data from trials of brain implants could help researchers to develop noninvasive therapies for mental illnesses that stimulate the brain through the skull. "The exciting thing about these technologies," he says, "is that for the first time we're going to have a window on the brain where we know what's happening in the brain when someone relapses."

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—SARA REARDON

NEWS

Talking with—Not Just to—Kids Powers How They Learn Language

Back-and-forth exchanges build the brain's language center and verbal ability

GETTY IMAGES

Children from the poorer strata of society begin life not only with material disadvantages but cognitive ones. Decades of research have confirmed this, including a famous 1995 finding by psychologists Betty Hart and Todd Risley: By age four children reared in poverty have heard 30 million fewer words, on average, than their peers from wealthier families. That gap has been linked to shakier language skills at the start of school, which, in turn, predicts weaker academic performance.

But the sheer quantity of words a toddler hears is not the most significant influence on language acquisition. Growing evidence has led researchers to conclude quality matters more than quantity, and the most valuable quality seems to be back-and-forth communication—what researchers variously call conversational turns, duets or contingent talk.

A paper published in February in *Psychological Science* brings a new dimension of support to this idea, offering the first evidence these exchanges play a vital role in the development of Broca's area, the brain region most closely associated with producing speech. Further, the amount of conversational turns a child experiences daily

But the sheer quantity of words a toddler hears is not the most significant influence on language acquisition.

outweighs socioeconomic status in predicting both activity in Broca's area and the child's language skills.

The study, from the lab of neuroscientist John Gabrieli of the Massachusetts Institute of Technology, involved 36 children, ages four to six, from a range of socioeconomic backgrounds. It had three components: First, researchers used standardized tests to evaluate each child's verbal ability and derive a composite score. Second, the brain of each child was scanned using functional magnetic resonance imaging (fMRI) while the child listened to very short (15-second) stories. Lastly, adult-child communication at home was evaluated for two days using a state-of-the-art recording and analysis system called LENA (Language Environment Analysis) to measure adult speech, the child's utterances and their conversational turns—paired exchanges separated by no more than five seconds.

The researchers confirmed the classic 1995 finding that, overall, kids from wealthier families hear more words. And although their sample was small, they even confirmed the 30-million-word gap between the poorest and richest children. But what correlated most closely with a child's verbal score was not the number of words he or she heard but the number of conversational turns. And these exchanges were the only aspect of language measured by LENA that correlated with the intensity of activity seen in Broca's area during the fMRI story session. "We found that by far the biggest driver for brain development was not the number of words spoken but the conversations," Gabrieli says. And although on average parents with greater income and education have more of

these verbal exchanges with their young children, "there's pretty good diversity," he notes. In other words, some low-income parents engaged in a lot of conversation with their child, and some wealthier parents conversed relatively little.

The researchers calculated that a child's verbal ability score increased by one point for every additional 11 conversational exchanges per hour.

How exactly exposure to these exchanges alters Broca's area is a question Gabrieli's team is exploring in subsequent research. "We know that greater activation in Broca's area was associated with better verbal abilities overall, so it seems like greater activation is good," he says. One possibility is back-and-forth communication promotes more connections between brain cells in that region.

The study is a "very, very important" addition to a growing body of work, says developmental psychologist Kathryn Hirsh-Pasek, director of the Infant Language Laboratory at Temple University, who was not involved in the work. "We have known for quite a while that conversational turns—or what in my work we call conversational duets—are very important for building a foundation for language and maybe for learning generally. What hadn't been done is to link it where we knew it had to be linked—to changes in the brain."

The search is on for interventions that will increase adult-child conversation and boost early language skills, especially for families.

Verbal exchanges have two components that children must master: temporal contingency and semantic contingency—essentially, understanding the timing of human conversation and how to respond meaningfully. Research, including Hirsh-Pasek's, has shown children cannot learn this from watching television, although they can learn it via video-chat technology such as Apple's FaceTime.

Contingent language begins in infancy—well before words emerge—when parents begin cooing and gooing at their babies, who respond in kind. Socioeconomic differences in this behavior arise during the first year of life, according to a 2017 study of 141 11-month-olds by Michelle McGillion of the University of Sheffield in England and her colleagues.

Research in this area has big implications for parents and caregivers. The search is on for interventions that will increase adult-child conversation and boost early language skills, especially for families living in poverty. McGillion's study, for instance, showed language learning took off for babies in low-income settings when caregivers were given instructions to spend 15 minutes a day engaging their infant by commenting on whatever the baby looked at. Unfortunately, the improvements did not persist at age two with this low-intensity intervention.

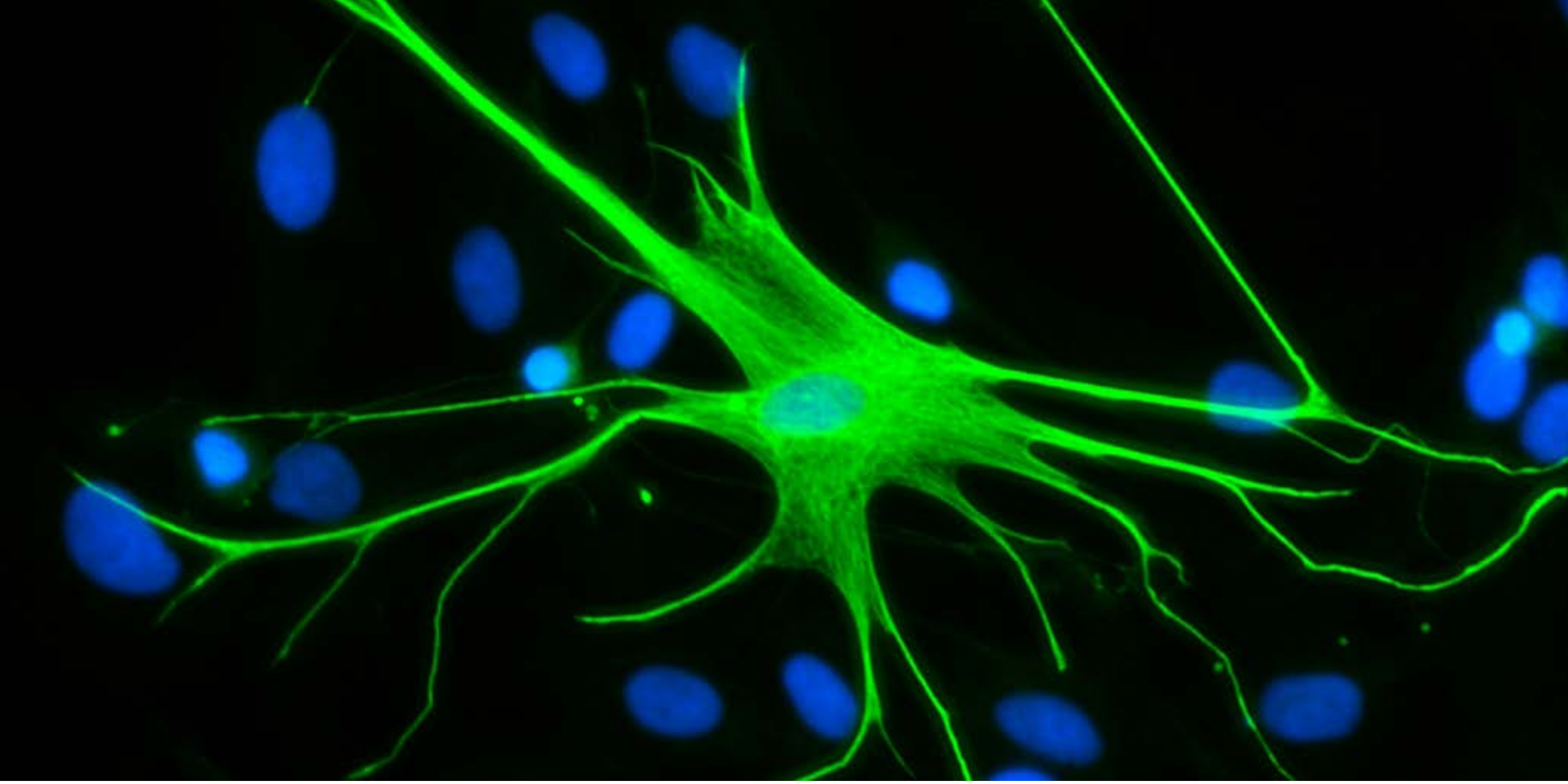
Encouraging conversation seems particularly necessary in an era when both children and adults are spending more time

with devices and less in face-to-face communication. “The exchanges are not only about words but about feelings, about paying attention to someone else,” Gabrieli observes. Hearing language from television or Alexa, he says, “does very little compared to these exchanges.”

Hirsh-Pasek shares this concern about technology. One 2017 study she co-authored found that when a cell-phone call interrupts an interaction in which a parent is teaching a child a new word, the learning is lost.

While we are fiddling with our digital devices, “evolution is screaming at us,” she says. “It’s saying, ’Hey, in case you didn’t notice, there’s another human in the room—pay attention.’ If we learn better how to follow the eyes of our child and comment on what they are looking at, we will have strong language learners. And language is the single-best predictor of school readiness—in math, social skills and reading skills. It is the foundation for learning.”

— CLAUDIA WALLIS



RICCARDO CASSIANI-INGONI *GETTY IMAGES*

NEWS

Getting to the Root of the Problem: Stem Cells Are Revealing New Secrets about Mental Illness

A fresh wave of research involves reprogramming ordinary skin cells into those found in the brain

Millions of Americans who suffer from bipolar disorder depend on lithium. The medication has been prescribed for half a century to help stabilize patients' moods and prevent manic or depressive episodes. Yet what it does in the brain—and why it does not work for some people—has remained largely mysterious.

But last year San Diego–based researchers uncovered new details about how lithium may alter moods, thanks to an approach recently championed by a small number of scientists studying mental illness: The San Diego team used established lab techniques to reprogram patients' skin cells into stem cells capable of becoming any other kind—and then chemically coaxed them into becoming brain cells.

This process is now providing the first real stand-ins for brain cells from mentally ill humans, allowing for unprecedented direct experiments. Proponents hope studying these lab-grown neurons and related cells will eventually lead to more precise and effective treatment options for a variety of conditions. The San Diego team has already used this technique to show some bipolar cases may have more to do with protein regulation than genetic errors. And another lab discovered the activity of glial cells (a type of brain cell that supports neuron function) likely helps fuel schizophrenia—upending the theory that the disorder results mainly from faulty neurons.

This new wave of research builds on Shinya Yamanaka's Nobel-winning experiments on cellular reprogramming from a decade ago. His landmark findings about creating induced pluripotent stem cells (iPSCs) have only recently been applied to studying mental illness as the field has matured. "What's really sparked that move now has been the ability to make patient-specific stem cells—and once you can do that, then all sorts of diseases become amenable to investigation," says Steven Goldman, who specializes in cellular and gene therapy at the University of Rochester Medical Center.

To get to the bottom of why lithium helps some bipolar patients, stem cell scientist Evan Snyder and his colleagues at the Sanford Burnham Prebys Medical Discovery Institute wanted to examine neuron formation—comparing samples from those who respond to the medication and those who do not. The team obtained ordinary skin cells from people in both groups and transformed those samples into iPSCs, and then brain cells. "When you reprogram cells into iPSCs, they lose all markers of age, regardless of how old the person is," says Kristen Brennand, a stem cell biologist at the Icahn School of Medicine at Mount Sinai, who was not involved in the work. "We can look at disease risk in a dish without any impact of things like drug abuse or adolescent trauma or infection of the mother while pregnant—so all we have is the genetic risk that was there when sperm met egg."

"When you reprogram cells into iPSCs, they lose all markers of age, regardless of how old the person is."—Kristen Brennand

With these lab-grown models, Snyder and his team were able to compare how neurons matured in the two bipolar groups. They could also scour the cells' molecular pathways for possible explanations about how lithium works and why. They ultimately found that a protein called CRMP2, which regulates neural networks and is found inside of cells, appears to play an outsize role in influencing whether or not lithium helps patients.

Lithium, they concluded, makes CRMP2 act normally. Apparently the protein acts sluggishly in some bipolar patients, hampering neurons' ability to form dendritic spines—little bumps that occur on the edges of nerve cells that are necessary for neural communication. The problem, the researchers found, is not caused by an abnormal gene or errors in the responsiveness of a gene—or even the amount of protein a gene makes. Instead it stems from changes to the shape, weight or electrical charge of the protein. This makes lithium-responsive bipolar disease the first confirmed mental health disorder fueled not by a genetic mutation but rather by hiccups in the "post-translational modification" of a protein, Snyder says. He suspects that cases of bipolar disorder that do not respond to the drug are actually a different disease altogether.

Looking at these findings, researchers may now try to develop lithium alternatives that similarly restore CRMP2 activity, but only act on that protein pathway—allowing patients to avoid problematic side effects that may come from lithium hitting inappropriate targets. (It can, for example, cause memory deficits and fine-motor-skill deficiencies.) Researchers have previously had some information about the brain pathway lithium works on, but Brennand notes gaps have remained. "Snyder has described another target of lithium, and this one might be more accurate," she says.

Creating Mini-Brains in the Lab

One problem in studying mental illness has always been that the brain is not very accessible while a patient is alive. Scientists have devised some ways around this: During the last decade genome-wide association studies have helped scientists link certain genetic mutations to specific disorders, for example. But that work left many mysteries about the causes of mental illnesses including schizophrenia, autism and bipolar disorder, which are all related to many genes. Animal studies can often help, but scientists cannot know if a mouse bred to have certain characteristics of schizophrenia is truly a schizophrenic mouse.

Work with induced pluripotent stem cells has helped change how clinicians think about schizophrenia. Goldman and some colleagues reported in August glial cells play a central role in the disorder. The researchers took iPSCs from schizophrenic and healthy subjects, turned them into glial progenitor cells and showed that only the ones from the mentally ill patients would alter the behavior of mice implanted with them. These mice developed symptoms similar to those of some humans with schizophrenia, including reduced inhibition, social isolation and excessive anxiety.

Tapping stem cells is particularly exciting because it can be coupled with traditional methods of studying mental illness, according to specialists in the field. For example, once researchers identify cells they think are significant, they can place them into mouse models (as Goldman did), seeing how they affect the behavior of these human-rodent chimeras. "In these cases, we are turning the mouse brain into

a living test tube," Goldman says. He notes scientists can also compare cells from a schizophrenic patient and a mentally healthy patient, and look for anatomical differences. "These technologies have given us a leg up we didn't have years ago," he adds. Researchers are also coupling iPSCs with gene-editing techniques to create cell populations with specific genetic mutations—or to determine whether specific genetic mutations cause certain problems—says Guo-li Ming, a neuroscientist at the University of Pennsylvania Perelman School of Medicine.

Ming was one of the first researchers to employ iPSCs to explore mental health disorders. Lately she and others have also been taking the field in another direction: using iPSCs to develop 3-D brain organoid models, essentially building mini-brains comprising different neural cells. These cells live and interact in a solution, recapitulating many unique features of human brain development. This allows scientists to study the cross-talk among different types of cells in the brain, a process that may be involved in mental health disorders, Ming says.

The tantalizing goals of all of this stem cell work, she says, are to create personalized medications for individual patients and be able to quickly screen existing drugs against patients' cells in the lab—determining whether doctors should send patients home with specific drugs. "Maybe in a decade or two we can achieve at least some of this," Ming says. Yet already, Snyder says, the new findings have opened an "entirely new epoch in research."

— DINA FINE MARON

NEWS

Getting the Inside Dope on Ketamine's Mysterious Ability to Rapidly Relieve Depression

The notorious party drug may act as an antidepressant by blocking neural bursts in a little-understood brain region that may drive depression

VOISIN *GETTY IMAGES*

Ketamine has been called the biggest thing to happen to psychiatry in 50 years, due to its uniquely rapid and sustained antidepressant effects. It improves symptoms in as little as 30 minutes, compared with weeks or even months for existing antidepressants, and is effective even for the roughly one third of patients with so-called treatment-resistant depression.

Although there are multiple theories, researchers do not quite know how ketamine combats depression. Now, new research has uncovered a mechanism that may, in part, explain ketamine's antidepressant properties. Two studies recently published in *Nature* describe a distinctive pattern of neural activity that may drive depression in a region called the lateral habenula (LHb); ketamine, in turn, blocks this activity in depression-prone rats.

Originally licensed as an anesthetic in 1970, ketamine has since gained fame as a party drug for causing out-of-body experiences, hallucinations and other psychosis-like effects. Its antidepressant properties in humans were discovered almost 20 years ago. Ketamine does not directly influence the same chemical messengers as standard antidepressants such as serotonin, but

Although there are multiple theories, researchers do not quite know how ketamine combats depression.

rather works via interaction with another chemical, glutamate—not usually associated with mood but rather with brain plasticity. One prominent idea about how it alleviates depression is by promoting the growth of new neural connections. "We provide a new angle for people to think about how this drug works," says neuroscientist Hailan Hu of Zhejiang University in China, leader of the team that conducted both studies. If she is right, her group may have identified multiple new lines of attack for treating a condition the World Health Organization calls the leading cause of disability worldwide.

Both new studies probe the workings of the LHb, a small, central brain region that acts like the dark twin of the brain's reward centers by processing unexpectedly unpleasant events. For example, if an animal has been trained to expect food when reaching the end of a maze and the reward is not there, the LHb activates, signaling a discrepancy between expectation and outcome. This has led to the LHb being dubbed the key part of a "disappointment circuit." If the LHb is overactive, it could suppress rewards from normally pleasurable activities—a symptom known as anhedonia—leading to long-term apathy and hopelessness. Studies in animals suggest hyperactivity in the LHb contributes to depression, but the details have been murky.

The first study, led by neuroscientist Yan Yang, also at Zhejiang, discovered a distinctive pattern of rapid bursts in the LHb of rats that display depressionlike behaviors. More usual neural activity, where neurons fire at spaced intervals, was not related to depression, suggesting it is burst ac-

tivity, rather than increased LHb activity per se, that is related to depression. Exactly why bursts are important is not clear, but the researchers think they may enhance communication with other regions. "It's like a machine-gun shooting versus single shooting, so it carries information more efficiently to downstream brain areas," Hu says. The team also provoked LHb neurons into burst firing using optogenetics, a technology that allows neurons to be activated with light. The results showed increased depressive behaviors, indicating the bursts actually cause depression rather than just occur alongside it.

The researchers stumbled on ketamine after they injected a drug that blocks NMDA receptors (for glutamate that, when activated, allow calcium to flood inside cells, causing them to fire) in the LHbs of depression-prone rats and saw strong antidepressant effects. Ketamine also blocks NMDA receptors, so the team repeated this with ketamine and again alleviated depression, within one hour. "We show that infusion of ketamine into just one brain region is sufficient to cause rapid antidepressant effects," Hu says. Studies of brain tissue samples showed that whereas ketamine silenced burst firing within minutes, the standard antidepressant fluoxetine hydrochloride, commonly known as Prozac, had no such effect at these timescales.

The second study, led by Zhejiang neuroscientist Yihui Cui, looked at what might cause burst firing in depression. The researchers found a protein, Kir4.1, was present at higher levels in depressive rats. Kir4.1 is found in cells called astrocytes, which influence neuronal activity. The team showed this protein promotes burst firing in LHb neurons. Raising Kir4.1 levels increased depressionlike behaviors, whereas blocking its function reduced them.

The studies do not reveal how burst firing influences depression, but the researchers have a hypothesis. The LHb connects to parts of the limbic system—which processes emotion—as well as reward centers that signal using chemical messengers associated with pleasure and mood, like dopamine and serotonin. The LHb inhibits activity in these regions, so burst firing may more effectively put the brakes on systems that produce reward signals from pleasurable activities. "Our results provide a simple model of how ketamine leads to disinhibition of the reward center to quickly relieve depression," Hu says.

Among researchers not taking part in the work, not everyone agrees the story can be this simple, however. "We've found the habenula is underactive in depressed patients, which is inconsistent with these data," says neuroscientist Jonathan Roiser of University College London. But if these discrepancies can be resolved, studying the LHb is a promising path toward entirely new approaches to treating severe depression. "It's fascinating to see that ketamine dampens habenular hyperactivity," says psychiatrist Matthew Klein of the University of California, San Diego. "Further research will show whether this is the rapid antidepressant mechanism in human patients."

The new findings have several implications for treatment. Understanding how ketamine acts so quickly could provide greater insight into the core mechanisms of depression and help to develop next-generation ketamine-based treatments that do not have the same side effects as the drug itself, such as dissociation and bladder problems. Several pharmaceutical companies have been pursuing this goal, but knowing what it is about ketamine that

produces the desirable effects could, in principle, aid these efforts.

Researchers are still studying ketamine's long-term effects, safety and optimum doses in clinical trials. Currently, patients are administered ketamine via infusions in a hospital, which, combined with the side effects, makes it unwieldy. "It would be great if we could reproduce ketamine's rapid effects in a simple oral medication," Klein says. "Its most exciting benefit is in treating suicidal ideation, which we currently don't have any fast-acting therapies for; it's an unmet clinical need that could save lives."

The recent work also identifies multiple new targets for therapies, including Kir4.1 and t-type voltage-sensitive calcium channels (t-VSCCs), another target implicated in burst firing. The team is planning to test whether drugs that block t-VSCCs have antidepressant effects, Hu says.

—SIMON MAKIN

SPECIAL REPORT

THE SCIENCE OF MEMORY

Surprising new findings are shaping how we understand this essential faculty of the mind

JONATHAN KNOWLES *GETTY IMAGES*

Portrait of a Memory

Researchers are painting intricate pictures of individual memories and learning how the brain works in the process

By Helen Shen

For someone who's not a *Sherlock* superfan, cognitive neuroscientist Janice Chen knows the BBC's hit detective drama better than most. With the help of a brain scanner, she spies on what happens inside viewers' heads when they watch the first episode of the series and then describe the plot.

Chen, a researcher at Johns Hopkins University, has heard all sorts of variations on an early scene, when a woman flirts with the famously aloof detective in a morgue. Some people find Sherlock Holmes rude while others think he is oblivious to the woman's nervous advances. But Chen and her colleagues found something odd when they scanned viewers' brains: as different people retold their own versions of the same scene, their brains produced remarkably similar patterns of activity.

Helen Shen is a science writer based in Sunnyvale, Calif. She has contributed to *Nature*, *Science* and the *Boston Globe*.

Memory, it turns out, is a highly distributed process, not relegated to any one region of the brain.

Chen is among a growing number of researchers using brain imaging to identify the activity patterns involved in creating and recalling a specific memory. Powerful technological innovations in human and animal neuroscience in the past decade are enabling researchers to uncover fundamental rules about how individual memories form, organize and interact with each other. Using techniques for labeling active neurons, for example, teams have located circuits associated with the memory of a painful stimulus in rodents and successfully reactivated those pathways to trigger the memory. And in humans, studies have identified the signatures of particular recollections, which reveal some of the ways that the brain organizes and links memories to aid recollection. Such findings could one day help to reveal why memories fail in old age or disease, or how false memories creep into eyewitness testimony. These insights might also lead to strategies for improved learning and memory.

The work represents a dramatic departure from previous memory research, which identified more general locations and mechanisms. "The results from the rodents and humans are now really coming together," says neuroscientist Sheena Josselyn of the Hospital for Sick Children in Toronto. "I can't imagine wanting to look at anything else."

In Search of the Engram

The physical trace of a single memory—also called an engram—has long evaded capture. Psychologist Karl Lashley was one of the first to pursue it and devoted much of his career to the quest. Beginning around 1916, he trained rats to run through a simple maze, and then destroyed a chunk of cortex, the brain's outer surface. Then he put them in the maze again. Often the damaged brain tissue made little difference. Year after year, the physical location of the rats' memories remained elusive. Summing up his ambitious mission in 1950, Lashley wrote: "I sometimes feel, in reviewing the evidence on the localization of the memory trace, that the necessary conclusion is that learning is just not possible."

COLIN ANDERSON *GETTY IMAGES*

Memory, it turns out, is a highly distributed process, not relegated to any one region of the brain. And different types of memory involve different sets of areas. Many structures that are important for memory encoding and retrieval, such as the hippocampus, lie outside the cortex—and Lashley largely missed them. Most neuroscientists now believe that a given experience causes a subset of cells across these regions to fire, change their gene expression, form new connections and alter the strength of existing ones—changes that collectively store a memory. Recollection, according to current theories, occurs when these neurons fire again and replay the activity patterns associated

with past experience.

Scientists have worked out some basic principles of this broad framework. But testing higher-level theories about how groups of neurons store and retrieve specific bits of information is still challenging. Only in the past decade have new techniques for labeling, activating and silencing specific neurons in animals allowed researchers to pinpoint which neurons make up a single memory.

Josselyn helped lead this wave of research with some of the earliest studies to capture engram neurons in mice. In 2009 she and her team boosted the level of a key memory protein called CREB in some cells in the amygdala (an area involved in processing fear) and showed that those neurons were especially likely to fire when mice learned, and later recalled, a fearful association between an auditory tone and foot shocks. The researchers reasoned that if these CREB-boosted cells were an essential part of the fear engram, then eliminating them would erase the memory associated with the tone and remove the animals' fear of it. So the team used a toxin to kill the neurons with increased CREB levels, and the animals permanently forgot their fear.

A few months later Alcino Silva's group at the University of California, Los Angeles, achieved similar results, suppressing fear memories in mice by biochemically inhibiting CREB-overproducing neurons. In the process, they also discovered that at any given moment, cells with more CREB are more electrically excitable than their neighbors, which could explain their readiness to record incoming experiences. "In parallel, our labs discovered something completely new—that there are specific rules by which cells become part of the engram," says Silva.

But these types of memory-suppression studies sketch out only half of the engram. To prove beyond a doubt that scientists were in fact looking at engrams, they had to produce memories on demand, too. In 2012 Susumu Tonegawa's group at the Massachusetts Institute of Technology reported creating a system that could do just that.

By genetically manipulating brain cells in mice, the researchers could tag firing neurons with a light-sensitive protein. They targeted neurons in the hippocampus, an essential region for memory processing. With the tagging system switched on, the scientists gave the animals a series of foot shocks. Neurons that responded to the shocks churned out the light-responsive protein, allowing researchers to single out cells that constitute the memory. They could then trigger these neurons to fire using laser light, reviving the unpleasant memory for the mice. In a follow-up study, Tonegawa's team placed mice in a new cage and delivered foot shocks, while at the same time reactivating neurons that formed the engram of a safe cage. When the mice were returned to the safe cage, they froze in fear, showing that the fearful memory was incorrectly associated with a safe place. Work from other groups has shown that a similar technique can be used to

tag and then block a given memory.

This collection of work from multiple groups has built a strong case that the physiological trace of a memory—or at least key components of this trace—can be pinned down to specific neurons, says Silva. Still, neurons in one part of the hippocampus or the amygdala are only a tiny part of a fearful foot-shock engram, which involves sights, smells, sounds and countless other sensations. "It's probably in 10 to 30 different brain regions—that's just a wild guess," says Silva.

A Broader Brush

Advances in brain-imaging technology in humans are giving researchers the ability to zoom out and look at the brain-wide activity that makes up an engram. The most widely used technique, functional magnetic resonance imaging (fMRI), cannot resolve single neurons but instead shows blobs of activity across different brain areas. Conventionally, fMRI has been used to pick out regions that respond most strongly to various tasks. But in recent years, powerful analyses have revealed the distinctive patterns, or signatures, of brain-wide activity that appear when people recall particular experiences. "It's one of the most important revolutions in cognitive neuroscience," says Michael Kahana, a neuroscientist at the University of Pennsylvania.

Conventionally, fMRI has been used to pick out regions that respond most strongly to various tasks.

The development of a technique called multi-voxel pattern analysis (MVPA) has catalyzed this revolution. Sometimes called brain decoding, the statistical method typically feeds fMRI data into a computer algorithm that automatically learns the neural patterns associated with specific thoughts or experiences. As a graduate student in 2005 Sean Polyn—now a neuroscientist at Vanderbilt University—helped lead a seminal study applying MVPA to human memory for the first time. In his experiment, volunteers studied pictures of famous people, locations and common objects. Using fMRI data collected during this period, the researchers trained a computer program to identify activity patterns associated with studying each of these categories.

Later, as subjects lay in the scanner and listed all the items that they could remember, the category-specific neural signatures reappeared a few seconds before each response. Before naming a celebrity, for instance, the celebrity-like

activity pattern emerged, including activation of an area of the cortex that processes faces. It was some of the first direct evidence that when people retrieve a specific memory, their brain revisits the state it was in when it encoded that information. "It was a very important paper," says Chen. "I definitely consider my own work a direct descendant."

Chen and others have since refined their techniques to decode memories with increasing precision. In the case of Chen's *Sherlock* studies, her group found that patterns of brain activity across 50 scenes of the opening episode could be clearly distinguished from one another. These patterns were remarkably specific, at times telling apart scenes that did or didn't include Sherlock, and those that occurred indoors or outdoors.

Near the hippocampus and in several high-level processing centers such as the posterior medial cortex, the researchers saw the same scene-viewing patterns unfold as each person later recounted the episode—even if people described specific scenes differently. They even observed similar brain activity in people who had never seen the show but had heard others' accounts of it.

"It was a surprise that we see that same fingerprint when different people are remembering the same scene, describing it in their own words, remembering it in whatever way they want to remember," says Chen. The results suggest that brains—even in higher-order regions that process memory, concepts and complex cognition—may be organized more similarly across people than expected.

Melding Memories

As new techniques provide a glimpse of the engram, researchers can begin studying not only how individual memories form, but how memories interact with each other and change over time.

At New York University, neuroscientist Lila Davachi is using MVPA to study how the brain sorts memories that share overlapping content. In a 2017 study with Alexa Tompary, then a graduate student in her lab, Davachi showed volunteers pictures of 128 objects, each paired with one of four scenes—a beach scene appeared with a mug, for example, and then a keyboard; a cityscape was paired with an umbrella, and so on. Each object appeared with only one scene, but many different objects appeared with the same scene. At first, when the volunteers matched the objects to their corresponding scenes, each object elicited a different brain-activation pattern. But one week later neural patterns during this recall task had become more similar for objects paired with the same scene. The brain had reorganized memories according to their shared scene information. "That clustering could represent the beginnings of learning the gist of information," says Davachi.

Clustering related memories could also help people use prior knowledge to learn new things, according to research by neuroscientist Alison Preston of the University of Texas at Austin. In a 2012 study, Preston's group found that when

some people view one pair of images (such as a basketball and a horse), and later see another pair (such as a horse and a lake) that shares a common item, their brains reactivate the pattern associated with the first pair. This reactivation appears to bind together those related image pairs; people who showed this effect during learning were better at recognizing a connection later—implied, but never seen—between the two pictures that did not appear together (in this case, the basketball and the lake). "The brain is making connections, representing information and knowledge that is beyond our direct observation," explains Preston. This process could help with a number of everyday activities, such as navigating an unfamiliar environment by inferring spatial relationships between a few known landmarks. Being able to connect related bits of information to form new ideas could also be important for creativity or imagining future scenarios.

In a follow-up study, Preston has started to probe the mechanism behind memory linking and has found that related memories can merge into a single representation, especially if the memories are acquired in close succession. In a remarkable convergence, Silva's work has also found that mice tend to link two memories formed closely in time. In 2016 his group observed that when mice learned to fear foot shocks in one cage, they also began expressing fear toward a harmless cage they had visited a few hours earlier. The researchers showed that neurons encoding one memory remained more excitable for at least five hours after learning, creating a window in which a partially overlapping engram might form. Indeed, when they labeled active neurons, Silva's team found that many cells participated in both cage memories.

> "Our memory is not just pockets and islands of information."—Sheena Josselyn

These findings suggest some of the neurobiological mechanisms that link individual memories into more general ideas about the world. "Our memory is not just pockets and islands of information," says Josselyn. "We actually build concepts, and we link things together that have common threads between them." The cost of this flexibility, however, could be the formation of false or faulty memories: Silva's mice became scared of a harmless cage because their memory of it was formed so close in time to a fearful memory of a different cage. Extrapolating single experiences into abstract concepts and new ideas risks losing some detail of the individual memories. And as people retrieve individual memories, these might become linked or muddled. "Memory is not a stable phe-

nomenon," says Preston.

Researchers now want to explore how specific recollections evolve with time, and how they might be remodeled, distorted or even recreated when they are retrieved. And with the ability to identify and manipulate individual engram neurons in animals, scientists hope to bolster their theories about how cells store and serve up information—theories that have been difficult to test. "These theories are old and really intuitive, but we really didn't know the mechanisms behind them," says Preston. In particular, by pinpointing individual neurons that are essential for given memories, scientists can study in greater detail the cellular processes by which key neurons acquire, retrieve and lose information. "We're sort of in a golden age right now," says Josselyn. "We have all this technology to ask some very old questions."

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Foresee and Forget: How to Remember the Future

Thanks to memory, we are able to recall the past. But we also need it to implement new ideas in the future

By Matthias Kliegel and Nicola Ballhausen

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We're all familiar with the following scenario: You use the last pat of butter at breakfast and make a mental note to go to the store after work. Next morning, you realize your best intentions weren't enough to put butter on the table.

When was the last time you forgot something? Posing the question makes it clear our memory often leaves us in the lurch. We forgot to buy something, call someone, take a medication, send a letter or attach a file to an e-mail. What do all these situations have in common? In each case, it is something we decided to do seconds, minutes, hours or even days ago. Although this form of memory often presents problems in daily life, neuroscientists and psychologists have only been researching this phenomenon as an independent area of memory for about 40 years.

We need this prospective memory (also called memory for intentions) so we can remember to do things in the future in a timely manner. In this sense it differs from other phenomena that have been the subject of classical memory research for decades, which may be characterized as retrospective memory. The latter makes it possible for us to recall knowledge or earlier experiences; prospective memory, on the other hand, enables us to bring to mind future intentions. Retrospective memory is useful in recalling previously stored information as required—for example, when being asked to so on a memory test. In prospective memory that aspect of explicitly prompting memory retrieval is missing, because in everyday life no one else is usually there in real time to remind us to retrieve our intentions. What makes this type of memory so tricky is that *we* have to remember that the market we pass on the way home is supposed to remind us of what we need to get in the first place.

Prospective memory is crucial for two reasons: First, it is the type of memory that poses the most problems for us in everyday life. Studies have shown that as many as two-thirds of memory glitches may be attributed to failures of prospective memory. At the same time, we need it to come to terms with our everyday circumstances. It is important to remember to take a medication, congratulate a friend on her birthday or get to a business meeting on time. That is what prospective memory enables us to do. If we could not recall such future in-

Matthias Kliegel is a professor of cognitive aging research at the University of Geneva, where he is also director of the Center for the Interdisciplinary Study of Gerontology and Vulnerability (CIGEV). Although he has been researching prospective memory for 20 years, not a day goes by when he doesn't forget something.

Nicola Ballhausen is a psychologist and works as a senior postdoctoral researcher in Kliegel's department and at the CIGEV. She heads a team that researches cognitive control processes and their development in old age. One of her preoccupations is the techniques that might be used to improve prospective memory.

HANS-BERNARD HUBER *GETTY IMAGES*

tentions, we could not live autonomous and independent lives. To the extent that we are unable to remember prospectively, we will need help because such memory lapses are dangerous, for example, when we forget food cooking on the stove. Problems of this sort are one of the reasons why senior citizens or persons with a brain disorder may need a caregiver or institutionalization.

If prospective memory is so important, why has it taken so long for researchers to focus on it? The reason is that they considered situations in which prospective memory comes into play merely as everyday examples of other areas of memory. Among other things, they thought remembering items to be done, such as shopping, consisted merely of saving and then later recalling such items, as is the case with other short-term or long-term memory tasks. Simply knowing the items on a to-do list is not sufficient, however. One also has to *remember* one has to go to the store.

Many Possible Sources of Error

Researchers now distinguish between two components of prospective memory: a retrospective component that is very similar to traditional memory and relates to the content of an intention (remembering *what* one needs to do), and a prospective component (recalling in a timely manner *that* one needs to do something). Problems may occur with both components. For example, we may forget to act on an intention at the right moment if we are preoccupied with something else. This is an example of a lapse in the prospective component. Or we may become aware at a meeting that we can no longer recall all of the points we wanted to bring up, a failure of the retrospective component.

Interestingly, adults are relatively good at remembering what they want to do but may have problems actually doing it at the right time. In other words, the prospective dimension seems to pose problems for which few remedies have yet been found. What good is a shopping list if we find it unused in our pants pocket after we get home?

What good is a shopping list if we find it unused in our pants pocket after we get home?

Psychologists Mark McDaniel of Washington University in St. Louis and Gilles Einstein of Furman University have suggested two potential mechanisms by which people carry out their intentions: First, we may actively try to remember something at the right time. We will do everything we can not to forget the critical moment, especially if something personally important is at stake. We look at our watch regularly so the cake doesn't burn in the oven or we don't miss an important meeting. But it can also happen that an intention suddenly springs to mind, although we hadn't really thought about it much before.

We do not know exactly how this second mechanism works. It may be that something in our surroundings suddenly reminds us of our plan via association, such as recalling buying cupcakes when passing a coffee shop ad down the street. Although this passive mechanism functions relatively effortlessly, the more active version requires attention that must be withdrawn from other tasks, some of which may also be important. As we would expect, it is therefore more difficult and more prone to failure than the passive mechanism. Because many of the tasks we need to do are so important, we must rely on the active mechanism. This is one of the reasons why people working in situations that are heavily dependent on prospective memory, such as air traffic controllers, work short shifts and take lots of breaks.

Neuroscientists have now shown where in the brain these two pathways for implementing intentions are located. When the active mechanism is in play, networks in the anterior prefrontal cortex are activated. This area is involved especially when our attention is directed to something new. The other pathway makes use of networks located in the parietal and ventral regions that, among other things, are involved in autobiographical memory and the discovery of relevant visual stimuli.

Prospective memory is so important to

navigating daily life that it is important to understand whether it decays with age—and if so, how. We are attempting to do just that in our laboratory in Geneva, Switzerland, at the Center for the Interdisciplinary Study of Gerontology and Vulnerability (CIGEV). Fergus Craik, a pioneer in cognitive memory psychology at the Rotman Research Institute in Toronto provided the impetus for this research. As early as the mid-1980s he made the assumption prospective memory in particular becomes more unreliable in older persons, because it requires a great deal of attention. This assumption was later confirmed in many experiments in which the test subjects were asked to recall previously agreed-to tasks (for example, to press a button as soon as a certain word was said). Yet, in some studies, younger and older persons performed about the same—there were even a few where older subjects did better. More and more researchers began to get involved in the study of prospective memory to resolve this contradiction. And they brought an unusual phenomenon to light: the age-prospective-memory paradox.

And does prospective memory become less reliable with age or does it not?

When Elders Do Better

If we test subjects at home with everyday tasks (for example, remembering to call someone twice a day), older people do better than younger ones—although the effect is precisely the opposite in the laboratory. This finding raises two important questions, which our team and colleagues throughout the world are examining: How is the odd discrepancy between laboratory and everyday life to be explained? And does prospective memory become less reliable with age, or does it not?

Tasks performed under laboratory conditions and those performed in daily life differ in various ways. In the laboratory memory is usually tested using standardized tasks that require multitasking. Under these conditions test subjects are generally unable to come up with mnemonic devices or use such memory aids as kitchen timers or to-do lists. For example, participants may be asked to look at a video and press a button every five minutes, tasks that have no intrinsic meaning to them. This may well be why they perform less well in the laboratory than out in the world, where priorities must be established and forgetting can have real consequences. In addition, the time span over which test subjects must retain something in memory is considerably shorter than it is in everyday life.

At the same time, the lives of younger and older people are not really comparable. The former are often engaged in study, must manage a variety of tasks and

navigate unexpected situations; the lives of the latter are usually more predictable and follow a less chaotic rhythm. This circumstance makes it easier to remember. In addition, younger people may be more used to laboratory tests or feel less stressed in this setting. We also cannot rule out that an exaggerated self-image may play a role in the age paradox. Although both age groups underestimate their prospective abilities in the lab, only the younger participants tended to overestimate their performance in their usual, familiar environment. This may lead to their being less well prepared for a task.

Does prospective memory decrease as we age? If we focus only on laboratory experiments the situation is clear: This area of memory, too, becomes less reliable with age. Studies done in people's own environments, however, have shown the capacity we need to maintain our daily lives remains intact for quite a long time, as long as we stay healthy. We are not yet able to answer the question conclusively, because too few studies have been conducted on the performance of different age groups in everyday life.

Future research must examine at least three dimensions of prospective memory: First, more experiments are needed on everyday life. Only sophisticated methods that do not interfere with the daily lives of test subjects will enable us to measure their prospective memory in a natural setting. Second, we must closely examine noncognitive factors such as motivations, emotions and stresses in order to understand this memory system. Finally, understanding the age-prospective-memory paradox may provide an opening for research aimed at maintaining certain cognitive processes and even improving them over the life span. There is some reason to hope a change in perspective from the deficits experienced by older people to the capacities that remain intact may change considerably our image of aging.

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Brain "Pacemaker" Could Help You Remember Only What You Might Forget

An implant is the latest development in research on neural stimulation to boost cognition

By Dana G. Smith

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Imagine if when you tried to learn something new, whether a person's name or your 15th e-mail password, your brain received an electrical boost. This little jolt of electricity would shock neurons into action and make them pay attention, increasing your likelihood of being able to recall the information when you needed it.

This type of implantable neural device is no longer purely science fiction—or an episode of *Black Mirror*. Scientists have developed an apparatus that will electrically nudge the brain when it seems at risk of forgetting new information. The technology, which combines a technique called deep-brain stimulation (DBS) with real-time monitoring of neural activity, improved participants' performance on a memory task by as much as 15 percent.

In DBS an electric current is delivered to the brain via electrodes implanted at strategic locations. The device has helped to control tremors in patients with Parkinson's disease and stop seizures in those with severe epilepsy. Scientists are now exploring whether DBS might even help treat Alzheimer's disease. But early studies of DBS's effect on memory have been mixed—some tests led to a boost in performance, whereas others resulted in impairment.

The different outcomes seem to depend largely on where and when the stimulation occurs. In the new study, published in *Nature Communications*, senior author Michael Kahana wanted to let the brain's own activity guide the stimulation. "I've been studying the electrophysiology of memory processes for many years, and it seemed to me that [we should] use the electrical signals of the brain that predict good memory to help teach us how to stimulate the brain," says Kahana, who is a professor of psychology at the University of Pennsylvania.

Kahana's team first had to determine what good memory function looked like. To do so, the researchers enlisted 25 epilepsy patients who already had electrodes implanted in their brains to monitor their seizures. The researchers used the electrodes to measure neural activity while the patients memorized lists of words. They then compared brain activity for words the patients recalled correctly versus words they forgot. Activity in an area of the brain called the lateral temporal cortex, which is part of the core memory network, seemed to predict whether or not a patient would later remember the word.

The researchers then developed software that could tell in real time whether activity in this part of the brain was optimal for remembering or not. If the software detected the brain was in a poor learning state, it triggered a small electric pulse to stimulate the area. The electric current in DBS is typically constant,

Dana G. Smith is a freelance science writer specializing in brains and bodies. She has written for *Scientific American*, the *Atlantic*, the *Guardian*, NPR, *Discover*, and *Fast Company*, among other outlets. In a previous life, she earned a Ph.D. in experimental psychology from the University of Cambridge.

but this closed-loop system acts more like a pacemaker, only zapping the brain when stimulation is needed. "We're inducing neural activity within the core memory network at a time when the network has quieted down but it should not have," Kahana says.

Although the study was done in patients without memory impairment, hope for using DBS to treat dementia is mounting—especially because the most promising pharmaceutical clinical trials for Alzheimer's continue to disappoint. "I think it's a really exciting finding," says Gwenn Smith, a professor of psychiatry and behavioral sciences at Johns Hopkins University who was not involved in the work. "The study was very methodologically elegant and has a lot of potential for treating memory disorders."

Itzhak Fried, a professor of neurosurgery at the University of California, Los Angeles, who also did not participate in the study, agreed the findings were promising but wanted to see more evidence for clinical impact. "In principle, stimulation which is based on some neural feedback from the brain offers advantages over standard DBS, which is a one-way street," he wrote in an e-mail. "However, it remains to be seen if this method will yield better results."

The closed loop is good for things that occur over a short time frame—seconds.

Andres Lozano, chair of neurosurgery at the University of Toronto who, with Smith, has conducted several clinical trials using DBS in Alzheimer's patients, says the advantages of using intermittent versus constant stimulation depend on the desired outcome. "The closed loop is good for things that occur over a short time frame—seconds. If you're interested in things that occur over days or years, then it's not entirely clear that closed loop is the most beneficial," he says.

In one trial by Lozano and Smith, Alzheimer's patients over the age of 65 who received continuous DBS had less cognitive decline over the course of a year than patients who did not receive it. DBS also resulted in higher brain glucose metabolism, which Lozano says is a sign of improved functioning in neurons. Another study in mice showed DBS can reduce the presence of amyloid plaques and tau tangles in the brain—the neurological signatures of Alzheimer's that are thought to be behind neurodegeneration. "If the objective is to slow down the progress of Alzheimer's, then we may want to stimulate continuously," Lozano says. "We're tapping into the brain's endogenous repair and growth mechanisms, and stimulation can mobilize those mechanisms."

Other researchers want to take brain implants even further. Scientists at the

University of Southern California and Wake Forest University are attempting to build a "memory prosthesis" to produce the electrical signals associated with memories and feed them to the brain. Using electrodes, computers and complex mathematical models, they are working to decode the brain activity during learning and memory so they can recreate the signals if they're forgotten. So far, the scientists have succeeded in creating memory-related signals from learning activity in rats and monkeys, but they have not yet tested the technology in humans.

In the meantime closed-loop stimulation systems are becoming a reality. The company NeuroPace offers an FDA-approved device to treat epilepsy. The implants detect activity in the brain that predicts a seizure and then delivers an electric pulse to stop the seizure immediately.

Although the research to date has all been framed around improving memory in patients, the idea of enhancing cognition in those of us who just need a little boost is not far behind. Bryan Johnson, CEO of neurotech company Kernel, has said these types of brain prostheses could one day improve cognition in all of us.

Fried, the U.C.L.A. neurosurgeon, dismisses the idea of using deep-brain stimulation for something as trivial as remembering names at a cocktail party. "This is invasive technology designed to treat impairment and alleviate suffering of neurological patients, and is a medical procedure which should be guided and regulated by stringent clinical criteria," he wrote.

Kahana is more open to the idea, however. "I think there's a lot of concern that invasive technology is too risky to imagine being deployed at a very large scale. You could imagine that people would be reluctant to have brain surgery to get a device that would improve their cognitive function," he says. "But brain surgery for this kind of technology is becoming safer and safer and safer every year. [One day] the so-called invasive technologies could become sufficiently low-risk [so] that we won't even think about them as being that invasive anymore." Cosmetic surgery is ho-hum routine—and so is LASIK. It still may take some time to get used to the idea of elective brain surgery. Who wants to go first? **M**

It still may take some time to get used to the idea of elective brain surgery.

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OPINION

To Combat Loneliness, Promote Social Health

Mounting evidence shows that relationships should be a public health priority

By Kasley Killam

In January the United Kingdom appointed a Minister for Loneliness to address the finding that nine million British people often or always feel lonely. To some, this may come as a surprise.

It should not. Loneliness and social isolation are on the rise, leading many to call it an epidemic. In recent decades the number of people with zero confidants has tripled, and most adults do not belong to a local community group. Consequently, more than one-third of Americans over the age of 45 report feeling lonely, with prevalence especially high among those under 25 and over 65 years old. "We live in the most technologically connected age in the history of civilization," writes former U.S. Surgeon General Vivek H. Murthy, "yet rates of loneliness have doubled since the 1980s."

While this alarming trend has grown, so has understanding of its impact. By now the evidence is abundant and decisive: social connection significantly affects health. When you believe that you have people in your life who care about you, and you interact with them regularly, you are better off. For instance, you may be less likely to catch a cold, have a stroke or heart disease, slip into early cognitive decline and develop depression. You may even be more likely to overcome socioeconomic disadvantages, recover quickly from illness and live longer. A study at Harvard University that followed hundreds of people for 75 years identified the quality of people's relationships as the single clearest predictor of their physical health, longevity and quality of life.

But the threat of loneliness is still largely absent from common health discourse, medical training and practice, and public awareness. It's time to establish a dedicated discipline to further study, develop initiatives around, and promote *social health*—how well a person forms and maintains relationships, receives and reciprocates support and feels connected to others. In the same way that mental health has risen up in prominence, yielding more and better research, treatment and advocacy, so too should social health.

Indeed, researchers led by Julianne Holt-Lunstad at Brigham Young University recently evaluated social connection using widely accepted public health criteria, including size, severity and urgency. They then compared it to well-established public health priorities that receive considerable resources across public and private sectors, such as nutrition. Despite not receiving similar resources, they concluded, social connection matches and in some cases exceeds other priorities in impact. (Other research suggests that loneliness has a comparable effect on health as smoking cigarettes daily and is worse than being obese or sedentary.)

Therefore, the authors propose that we take action by applying the same framework as existing public health priorities: First, convene experts to evaluate the literature periodically and make practical, evidence-based recommendations. Second, align on population-level measures to track progress, forecast problems and identify at-risk groups. Last, build coalitions that span the individual to the societal, including local health care settings, nonprofits and government agencies.

Already a social health movement is gaining momentum, with numerous initiatives pointing the way for future efforts to follow. Designating a minister to develop

Kasley Killam is the health care community engagement manager at Verily (formerly known as Google Life Sciences) and a World Economic Forum global shaper in San Francisco.

policies and catalyze innovation around the issue, as the U.K. has done, is an excellent example and will be interesting to follow in the years to come. But, as the researchers noted, it is important to diversify the approaches to bolstering social health.

For instance, the Togetherness Program created by CareMore, a health plan and delivery system in the U.S., is taking a medical approach. Sachin H. Jain, president of CareMore, has stated that loneliness "should be addressed by physicians, nurses, and other clinicians as a treatable medical condition." Among their efforts, they screen for loneliness during appointments, have regular phone conversations and home visits with at-risk senior patients to show they care, and provide informal social hubs at their clinics to foster connection.

The Campaign to End Loneliness takes a more grassroots advocacy approach. They have built up a network of more than 2,500 organizations and people in the U.K. who campaign to policy makers and commissioners. They actively spread awareness on social media, facilitate shared learning among the network members and partner with academics and specialists to make research actionable.

These initiatives mark the beginning of a shift toward seeing health as not only physical or mental, but also social. Elevating relationships in the public health realm through a variety of individual, community and societal efforts holds the potential to significantly improve population health. You can start exercising your own social health by calling a friend or family member you haven't spoken with in a while or introducing yourself to a neighbor you haven't met yet. It may just improve your health—and theirs. **M**

OPINION

What Makes Us Vibe?

We like other people in part because they think the way we do—but we may also think alike as a result of being friends

By Daniel Barron

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Think about your friends—the people you spend a lot of time with, see movies with, those people you'd text to grab a drink or dinner after a long week. Now think back to why you first became friends and ask yourself: was it because you *like* them? Or because you *are* like them? A recent study, led by Carolyn Parkinson, a psychologist at the University of California, Los Angeles, suggests that the answer may involve a complex network of brain regions that gets to the root of how friendship exists in our brains.

When I spoke with her, Parkinson told me that a key focus of her research is learning how social networks might shape or be shaped by how our brains process information. Her previous work explored how the brain encodes one's social standing, or where one sits in relation to another within a social hierarchy. She now wanted to understand how friendship itself was fleshed out in the brain.

Parkinson and her co-authors, Adam Kleinbaum and Thalia Wheatley of Dartmouth College, used a measure called social distance to define the friendship networks of 279 graduate students. Four months into their academic semester, Parkinson asked the students to consider an online list of their classmates and click on their friends. This Facebookian measure can be used to count how closely tied two individuals are based on their degree of social connection. Social distance, similar to six degrees of separation (or, alternatively, of Kevin Bacon), expresses how closely tied two individuals are within a larger social group.

Consider three people: Bill, Grace and Thomas. Bill and Grace are friends. Grace and Thomas are also friends. But Bill and Thomas have never met. In this scenario, Bill & Grace and Grace & Thomas are friends with one degree of separation while Bill & Thomas are two degrees of separation from each other (linked by their mutual friend Grace).

Parkinson used the questionnaire data to create a network that showed how far in social ties each of the students were from one another. These distances ranged from one degree of separation, meaning the students were friends with one another, to five degrees of separation, meaning that to draw a connection between two students in the friendship network, one would have to traverse a chain five friendships long.

Parkinson then showed 42 of the students a series of short video clips that resemble the way your TV would look if you were flipping through channels: three minutes of the earth from space, a few minutes of journalists debating, some slapstick comedy, a brief interlude watching a soccer match. Each student watched the same series of videos while their brain activity was recorded with functional MRI.

After the scan, Parkinson took the resulting MRI data and separated them based on where they originated in the brain. She then created what is known as a time series plot that represents how, on average, a brain region's activity changed as each student viewed the video sequence. With each time series plot in hand, Parkinson could then determine whether an individual's social relations were correlated with how their brain responded to viewing those videos.

Parkinson discovered that, indeed, the closer the social tie, the more similarly the student's brains responded to the videos. And interestingly enough, the brain regions

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Daniel Barron is a resident psychiatrist at Yale University. As a member of Yale's neuroscience research training program, he is helping to develop biomarkers for brain disease. Visit his Web site at www.danielsbarron.com

that were most similar across friends were those involved in attention and social cognition. The take-home: friends think alike.

These results fascinate me. If our engagement with social media is any indication, we spend an enormous amount of time thinking about our friends—about friends we have now, those we've had in the past, those we wish to have; the joys, the pains, the suspense of friendships. But I wager we don't often think about how that all happens, how beneath our veneer of consciousness, neural assemblies are churning through sensory information, trying to make sense of the world and struggling to understand how to act within it. Yes, we are a social species, so friendships and social ties are extremely important—but what does that mean? And how does that happen at the level of those neural assemblies? It turns out that our brains appear, in a very real way, to synchronize with people we befriend, an incarnation of social unity. Perhaps it's not simply that you *feel* close to your friends, but rather that you are *experiencing* the world more closely.

And of course I wondered which happens first. To (conversationally) binarize the question, I wondered about two chicken/egg scenarios: One, do we become friends with someone because their brain processes information like our own? Or two, does the act of befriending cause our brains to process information more similarly to our friends?

Parkinson was careful to remind me that because her study was cross-sectional—meaning she took a snapshot of the students and how their brains function—she can't draw conclusions regarding cause and effect. In other words, she can't say whether it was scenario one or two.

Either way, I see her results as an argument for some level of neural determinism. Consider the first scenario, wherein people with similar brains are drawn toward one another. This is an obvious case wherein your neurobiology has sculpted your social relationships. You may think you are choosing your friends, but your brain is really just responding to some neurophysiologic reflection; you see the world similarly, and so become friends.

The other scenario is a bit spooky. Say you somehow become friends with someone, perhaps by sitting next to them in class. As you get to know one another, you exchange some cognitive contagion that alters the way both of your brains perceive reality. By befriending, you become somehow not you.

It's probably a little bit of both; nature births chickens and eggs simultaneously. And given the fact that collectively, humans have been befriending one another for thousands of years, no neurological danger was revealed here. But still I wonder whether "falling into the wrong crowd" or "marrying up" has some neurological correlate. And what of interspecies friendships—do cat people and dog people's brains process information more like their pets? And vice versa? (I'm imagining the urge to stick my head out my car window.)

Fortunately Parkinson told me she is hard at work conducting a longitudinal study, one that follows people (which is to say human brains) from before they meet until they form friendships. So hopefully she'll give us an answer soon. In the meantime, choose your friends wisely. If you can. **M**

VINCENT BESNAULT GETTY IMAGES

OPINION

What Is "Normal," Anyway?

In psychology and psychiatry, it really means average or typical, but we too easily think of it as a synonym for how everyone is supposed to think and feel

By Jim Kozubek

I was in the modern agora of Walmart this winter when I started to lose it. I began to feel the onset of insanity, a sudden sense of depersonalization and an anticipation of impending doom. The more I tried to control it, alarmed at the spike in cortisol, the more acute the sensation was that I was losing consciousness and in serious danger. People continued shopping in the isles. One was throwing toothpaste in her cart. I was rapidly losing memory of basic procedural things, even who I am, of anything that happened even seconds ago.

This experience, commonly called a panic attack (if it makes you feel better to call it something), resolved in less than 15 minutes, against my belief that I was losing my mind, if not my life. I first noticed these acute events when I was about 20 years old. It did not help that at that time I was drinking heavily and often kept a Ziploc bag of psilocybin mushrooms in my jeans pocket. I was starting to become withdrawn. For a brief time I was put on a number of drugs, including the heavy-duty antipsychotic Zyprexa. Only after taking a thyroid replacement drug for a couple of years did my sense of well-being restore. I have not seen a psychiatrist or taken prescription or illegal drugs in two decades.

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It is easy to see how such acute events can turn into secondary symptoms. For instance, if you do not know when you might slip into a state of panic, or acute insanity, you may avoid social situations, and that can lead to excessive guilt, even mild depression. Last year I skipped out on an invitation to Tom Ashbrook's radio talk show *On Point*, live on WBUR. For a moment I felt terrible, as if I had let down my publisher, Cambridge University Press. But it turns out my publisher and Ashbrook's team did not make it into a big deal—and that enabled me to let it go. The positive social feedback loop made a difference, and that relates to the concept of low-expressed emotion, the value in other people's perception of such an event as transitory, or of little alarm.

A year ago I wrote an essay for the *Boston Globe* titled "Fixing Genes Won't Fix Us," which was deeply critical about the state of psychiatric genetics. Since I have a master's degree in genetics and have published some technical papers on schizophrenia and bipolar disorder, I figured I had at least some qualification to write such an essay, and it generated a lot of feedback. Since many people think I am antiscience or against biotech, I wanted to spend some ink to clarify my positions.

The first is that most genetic variants that influence psychiatric conditions only contribute to a weak effect, often less than a single percentage point on the risk of having such experience or condition. Many of these genetic variants are pleiotropic, meaning they have different enhancing or canceling effects on other genetic variants, or different effects in different cell types. Deleterious mutations can even stick

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Jim Kozubek is the author of *Modern Prometheus: Editing the Human Genome with Crispr-Cas9*, published by Cambridge University Press.

around in the population if they contribute to balancing selection, meaning they add to genetic diversity. In a broad sense of heritability, genetics influence endophenotypes—underlying psychology tendencies or traits—but nothing comes without trade-offs.

People with panic disorder are often more interoceptive, meaning they have an awareness of their heart beating (think Edgar Allan Poe) or their fluids moving, or their thoughts creaking; in effect, they often have a heightened degree of self-consciousness. In *The Noonday Demon*, Andrew Solomon wrote about one theory suggesting that depressive types are often more realistic than average.

Eminent poets and fiction writers, who have an acute sense of the transitory, are *more* apt to be bipolar or depressive, according to research by Arnold Ludwig in the 1990s. In *The Trip to Echo Spring*, Olivia Laing wrote of five writers, including Tennessee Williams, who as a young person on the streets of Paris became afraid of what he called "the process of thought" and came within "a hairsbreadth of going quite mad," describing his experiences as "the most dreadful, the most nearly psychotic, crisis that occurred in my early life." The point is not to venerate disorders through their connection to the arts—I would never do that—but to suggest the primal experience of human existence is a loss of control rather than a default of stability.

The progressive, neoliberal view that we can improve upon human nature is now widely accepted in the public consciousness.

Various studies suggest genetic mutations introduce a degree of risk, make us more sensitive or alter concentration, with effects that depend on the genetic background. One gene variant can lead to a fourfold reduction in the product of the gene *COMT*, which builds an enzyme that breaks down dopamine in the prefrontal cortex. The variant can lead to more dopamine, which can enhance concentration but also make you more neurotic or jittery. Such risk-benefit trade-offs are the reason I believe that autism and psychiatric disorders will be with us for the next thousand years. And yet we often hear fundraisers speak of hope for a cure for autism, for example. The progressive, neoliberal view that we can improve upon human nature is now widely accepted in the public consciousness. But it is possible that such disorders are nothing more than another way of coping with the realities of existence.

The concept of normal has a complicated history in medicine. In the 19th century the French physiologist Claude Bernard wrote of identifying statistical deviations from population norms to identify the causes of diseases. Around the same time, Jonathan Sholl writes in a recent essay in *Aeon*, Adolphe Quetelet applied "statistics to the human body to find a series of 'types' across a range of individual variations. Because every variation could be subject to this statistical tool, it seemed that averages could

explain anything: hence, height, weight, blood pressure, heart rate, birth and death rates etc. could all be presented in nice, even bell curves."

For instance, he invented the controversial body mass index (BMI). The average became the ideal, writes Sholl. "[T]he individual was synonymous with error, while the average person represented the true human being." The standards set by population averages are controversial. I have elevated levels of bilirubin, for example, a compound that breaks down heme, a product of red blood cells. My bilirubin is statistically high enough to be potentially harmful to my health, but other people in my family also have high bilirubin and suffer no undue effects.

In *Le Normal et le Pathologique* (1943), writes Sholl, French philosopher Georges Canguilhem "challenged the status quo of normality, suggesting it failed to capture what evolutionary biology says about variation. He sought to use the term norm to refer to the different processes, from the internal regulation of hormones to shifting dietary regimes, to remind us that, no matter how rare or deviant an individual seems, he could still be viewed as normal if the behavior ensured survival in a given environment." In 1978 Czech philosopher Jiří Vácha distinguished the meanings of normality; it could mean *frequent* (as a mode) or *average* (as a mean) in the population as represented in a typical bell curve. It could also mean *adequate* as in free from deficiency or defect or *optimal* in the sense of being physically fit or mentally sharp. The meaning of normal, Sholl writes, often "slip-slides among these different meanings and tropes, from the orthodox and standard to what is expected and good" and "has important consequences, especially if it is given a privileged position in the world."

Venture capital has a huge influence on scientists who want to develop drugs to sell to market.

For instance, the Stanley Center for Psychiatric Research at Broad Institute, which was started with a $650-million donation from Ted Stanley and family, appears to be mainly geared to advance scientific insight and monetize psychiatric disorders.

But scientific research continues to provide very few actionable biological targets, or to identify gene variants that contribute more than subtle effects on risk, while socioeconomic effects such as chronic arousal and physiological stress are major known factors. For instance, there is the fascinating insight into the allostatic, as compared to homeostatic, nature of human biology. As an example, blood pressure may shift its baseline based on social demands, so people who live in a state of poverty or have to cope with constant economic or social pressures may live in a chronic state of arousal; their baseline blood pressure may be higher.

The other important concept is the

inverted U, which suggests that elevation in stress is connected to creativity and peak performance, but that when stress becomes chronic, it can lead to a rapid collapse in productivity. This suggests how important socioeconomic influences are on health, psychology and even mortality. The recognition of genetic trade-offs and allosteric effects show that human biology exists along a dynamic continuum and defies categories inherent to the normalization of medicine. Nothing in evolution comes for free.

Genetics science may contribute to subtle insights in the genetics of psychiatric disorders, but it will certainly not lead to the elimination of psychiatric disorders, and it is not even likely to lead to a new generation of more effective drugs. If scientists make any advances in psychiatry, there is so far no reason to believe they will be anything but small steps, not big breakthroughs. The best thing that has emerged in recent years is ketamine, otherwise known as the street drug Special K, which stabilizes structural synaptic connections rather than correcting chemical imbalances.

If there are no strong singular genetic causes or biological targets, it is likely that the money spent on new drugs could be just as well spent for psychotherapy or other forms of social and economic support—but there is no business model for that.

So, it is not so much that I am against the venture vision of engineering our way out of psychological turmoil and despair, as I am *for* empathy that derives its effects from a decentralized position in nature, and for the concept of neurodiversity.

Canguilhem's interpretation of normalcy is compelling insofar as it provides a basis for the belief that psychiatric disorders are not deviations from the norm but expressions of attributes that can be normal in their contribution to human variation and persistence in the population. Autism, schizophrenia, depression and panic have been around since ancient times and will be around for thousands of years, if the subtle genetic variants that influence those conditions have some evolutionary use. People who live at the psychological margins of society challenge the privileged position of social norms and expose the reality of accidental qualities of human nature. Insofar as this is true, psychiatric disorders are not deviations from humanity as much as definitions of it. **M**

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OPINION

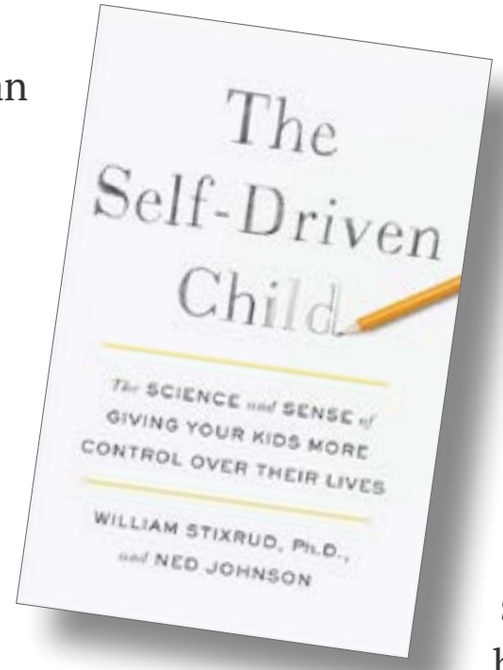
The Case for the Self-Driven Child

In a new book, an argument for giving children more of a sense of control over their lives

By Gareth Cook

We are raising the anxious generation, and the conversation about the causes, and the potential cures, has just begun. In *The Self-Driven Child*, authors William Stixrud and Ned Johnson focus on the ways that children today are being denied a sense of controlling their own lives—doing what they find meaningful, and succeeding or failing on their own. Screen time, the authors say, is part of the problem, but so are well-meaning parents and schools, who are unwittingly taking from children the opportunities they need to grow stronger, more confident and more themselves. Stixrud and Johnson answered questions from Mind Matters editor Gareth Cook.

What makes you think that children do not have enough control over their lives?
Stixrud: We know that a low sense of control is highly associated with anxiety, depression and virtually all mental health problems. Researchers have found that a low sense of control is one of the most stressful things that people can experience. And since the 1960s we've seen a marked rise in stress-related mental health problems in children and adolescents, including anxiety, depression and self-harm. Just in the last six or seven years, there has been an unprecedented spike in the incidence of anxiety and depression in young people.



From a neurological perspective, when we experience a healthy sense of control, our prefrontal cortex (the executive functioning part of our brain) regulates the amygdala (a part of the brain's threat detection system that initiates the fight or flight response). When the prefrontal cortex is in charge, we are in our right minds. We feel in control and not anxious. So, the fact that kids are feeling more anxiety, by definition, suggests that their amygdalas are more active, which indicates that they are more likely to feel overwhelmed, stuck or helpless.

Research on motivation has suggested that a strong sense of autonomy is the *key* to developing the healthy self-motivation that allows children and teens to pursue their goals with passion and to enjoy their achievements. But what we see in many of the kids we test or tutor is motivational patterns that are at the extremes of one, an obsessive drive to succeed and two, seeing little point in working hard. Many of these clients say that they feel overwhelmed by the demands placed on them, that they feel tired all the time, and that they don't have enough downtime in their lives (related, in part, to the increasing presence of technology). Many talk about the expectations that they feel they have to live up to, and many complain about the fact that they have little say over their own lives.

Is this a new problem?
Stixrud: It's one that has progressed over several decades. When psychologist Jean Twenge compared college students from the 1960s to college students in 2002, the latter reported a dramatically lower sense of control over their lives. Changes in our culture in the last 10 or 15 years appear to

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Gareth Cook is a Pulitzer Prize–winning journalist in Boston. He edits Mind Matters, an online commentary blog at www.ScientificAmerican.com/mind-matters

have contributed to an even sharper decline in a sense of control. For one, kids play much less than they did even a decade ago, as their time is taken up by more school hours, more scheduled activities and more screen time than ever before. Researcher Peter Gray was one of the first to connect fewer opportunities to play to a decline in a sense of control. When kids could spend most of their Saturday playing, they could choose their own games and how to play them. They had a lot more autonomy and a lot more agency than kids do today. A typical Saturday now is often packed with homework and organized sports events.

Also, for a whole host of reasons, ranging from technology to packed schedules to anxiety, kids today sleep much less than they did even a few years ago. Fifty percent of teenagers 15 years and older now sleep less than seven hours a night, whereas adolescents on average require 9 ¼ hours of sleep not to feel tired. When we don't get enough sleep, the connections between our prefrontal cortex and our amygdala are weakened, resulting in lower ability of the former to regulate the latter. When children are tired, they invariably experience a lowered sense of control, as they are more easily stressed, have reduced coping skills and are more apt to experience frustration and discouragement.

And studies have found that at least 10 percent of boys have an addictive relationship to video games.

Then there's technology, which obviously has grown ubiquitous. More kids are reliant on social media, and there may be nothing more externalizing or control-lowering than posting a photo of yourself on the Internet and waiting for people to judge you. A recent article by Twenge actually suggested that the smartphone and social media have likely contributed enormously to the dramatic increase in mental health problems seen in adolescents since 2012. And studies have found that at least 10 percent of boys have an addictive relationship to video games. Kids who are addicted to things often tell themselves, "I know I shouldn't be doing this but I can't stop," which is a pretty clear indicator that they lack a sense of control.

We agree with Twenge that this problem has been increasing since the 1960s because our culture has increasingly valued extrinsic and self-centered goals such as money, status and physical attractiveness, and devalued community, affiliation and the pursuit of meaning in life. Also, with technology driving an increasingly fast pace of life, it will only get worse unless we recognize how important having a sense of control is and make some changes.

How do attempts at controlling a child backfire?

Johnson: In addition to the physical and emotional consequences (more stress, anxiety and depression), trying to control a child has really negative effects on moti-

vation. According to one of the best supported theories in psychology, self-determination theory, humans have three basic needs: a sense of autonomy, a sense of competence and a sense of relatedness. Autonomy is built into our wiring, so to speak, in the same way as hunger or thirst. When we lack this basic need, we experience decreased motivation, or the motivation we do have becomes fear-based. ("I'd better do this, or else!") Both are terribly unhealthy. You can't become a self-driven person if you don't have a sense that your life is your own. We think the phenomenon of failure to launch—the preponderance of people in their 20s and 30s living at home—is in part attributable to the idea that young adults don't have the same drive for independence they used to have. They want to sit at home and play on their phones. They don't want to drive as much, date as much, have sex as much. They are accustomed to someone else being in charge of their life, and their internal motivation system is stymied.

There's another way to look at it, too. Evaluate what you gain when you try to control a child. Let's say you think your son—who struggles in math—should see a tutor all summer, and he disagrees. But you insist. It's possible that tutoring would help some, but the truth is that kids benefit very little from academic help they resist and don't feel they want or need. Even if it does help him, it comes at a great cost. It causes strain in your relationship with him. His competency *might* be improved, but his relatedness (his relationship with you) and his autonomy are lowered. Think of a three-legged stool where you make one leg longer and the other two shorter. You cannot reach higher on that stool. The most likely outcome is that it will tip over. And, you have signaled to him that you know better than he does, that his opinion doesn't matter. He also misses out on seeing what it's like to make decisions for himself. Kids need experience checking in with themselves and their decisions, and they can't do that if you're making each one.

Evaluate what you gain when you try to control a child.

Can you please explain the idea of home as a "safe base"?

Johnson: Just as in baseball, when you reach home base, you're in a place where you can catch your breath and not have to worry about being pegged with the ball or being called out, home should be a place for kids to rest and recover. They are facing stressors each day, from school demands to social dynamics. You want home to be the place they can go to seek a respite from it all, where they feel safe and loved unconditionally, where they can fully relax, so that they can gather the energy to go back out. But if home is a stressful environment—if parents are an anxious or controlling presence—kids will seek that respite somewhere—or somehow—else. And most of the time, it's a place you don't want them to go. Or, if nowhere can be that safe base, they are really in trouble, as being chronically stressed is about the worst thing imaginable for brains, es-

pecially developing ones. That's why we tell parents that one of the most important things they can say to their kids is, "I love you too much to fight with you about your homework," and why we want them to move in the direction of being a nonanxious presence for their kids.

What else can we do to give children more of a sense of self-control?

Johnson: We can give kids opportunities to learn to handle as much as they can without being overwhelmed. Children thrive and grow when they feel challenged but not threatened. Personal pastimes (especially when kids can turn up or down the pace or intensity themselves) are great for this. Think of how video games work: the better you can play and the further you advance, the harder the game gets. You don't actually die; you just have to try again. It's fantastic! Games can be incredibly frustrating but almost no one wants a "cheat code" to get ahead. It just doesn't offer the same satisfaction. In life, kids want to *feel* that their successes were earned. Give your kid every opportunity to stretch himself through music, sports, coding, after-school jobs, hiking, martial arts, whatever inspires his passion. That sense of mastery and autonomy in an activity he loves can cascade into other facets of his life.

You can nurture habits and a lifestyle that support healthy minds. Above all, promote rest. Encourage sleep, meditation if they're interested and downtime. Many of the students I see complain that the moment they have a free hour, their parent rushes in to fill it. Rest is not laziness. It is the basis of all activity. Foster what we call radical digital downtime. No phones. No screens. Those times of mind wandering (some call it boredom) activate neural circuits in the default mode network, a system that involves reflecting on the past and projecting into the future, processing life. Radical downtime increases the control that the prefrontal cortex exerts over the amygdala, keeping you in your "right mind."

Lastly, make it your highest priority to simply enjoy your kids. As they are. Right now. Flaws and all. For the development of babies, one of the most important inputs is parents who are warm and responsive. When do you think kids outgrow that need? We think, never. **M**

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