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BRAIN SECRETS TO STAYING YOUNG

An openness to new experiences can make you feel younger than your years

WITH COVERAGE FROM nature

PLUS

HOW KETAMINE CHANGES THE BRAIN

THE DARK TRIAD VS. THE LIGHT TRIAD OF PERSONALITY

DA VINCI'S ENDURING GENIUS

LIZ TORMES

A Fountain of Youth for Your Mind

Whether we want to or not, we all age. So it is no surprise that a vast consumer industry exists for all things antiaging—creams, diets, mantras, contraptions, pills, surgeries and legitimate prescription drugs. To be sure, a robust area of scientific research is devoted to the topic. One of the most interesting findings to emerge is that longevity is closely correlated with intelligence. This may be discouraging for those who never graduated from Oxford, considering raw intelligence is a relatively stable psychological trait and not easily amplified by any intervention. But as David Z. Hambrick writes in this issue, your attitude in life may count more than your smarts. A so-called openness to experience brings with it positive behaviors that improve your health and could extend your life (see "In Search of a (Subjective) Fountain of Youth").

Elsewhere in this issue, Simon Makin explores the ways that ketamine acts in the brain—first by changing brain circuit function and later by triggering the regrowth of brain synapses (see "Behind the Buzz: How Ketamine Changes the Depressed Patient's Brain"). And Jonathan Pevsner reflects on the genius—and limitations—of Leonardo da Vinci and wonders whether the Renaissance man would thrive in today's society (see "The Mind of Leonardo da Vinci"). As always, enjoy!

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On the Cover

An openness to new experiences can make you feel younger than your years

UCSF

WHAT'S INSIDE

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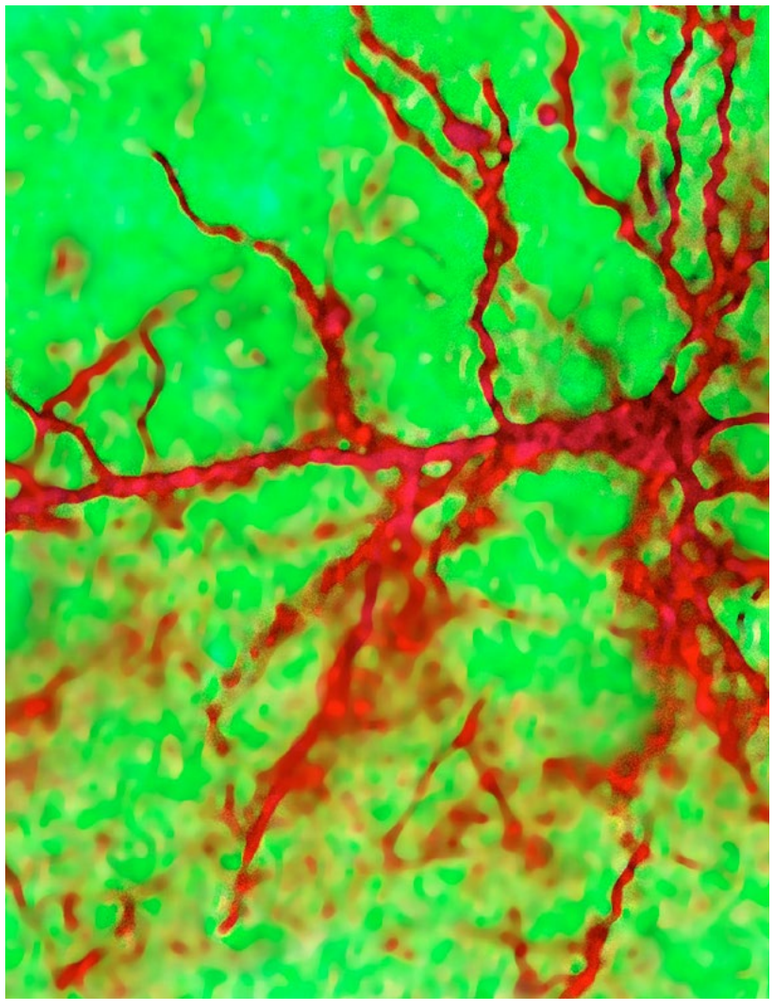

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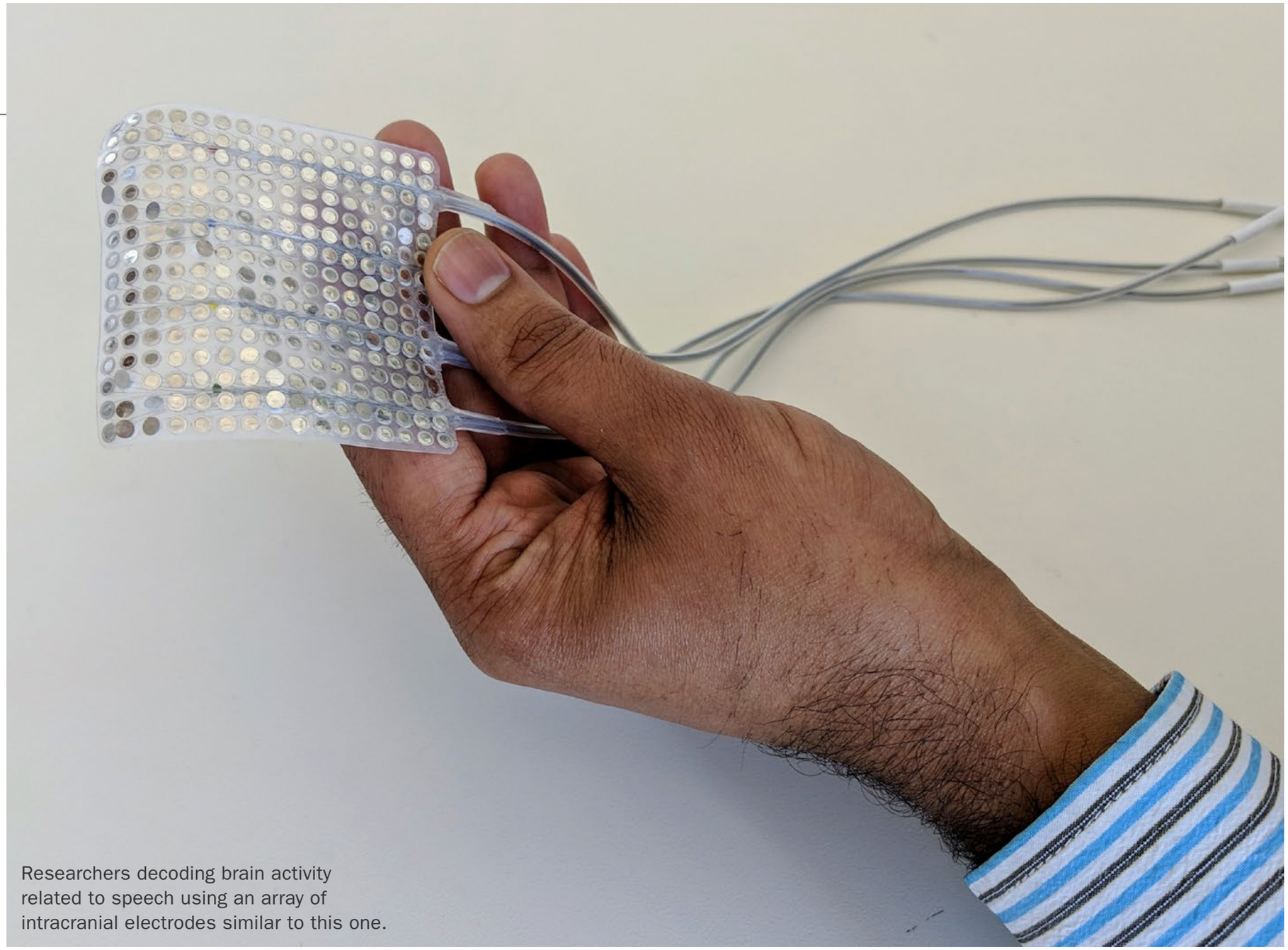
NEWS

Scientists Take a Step Toward Decoding Speech from the Brain

New study gets closer to restoring natural communication for those who cannot speak



Researchers decoding brain activity related to speech using an array of intracranial electrodes similar to this one.

STROKE, AMYOTROPHIC lateral sclerosis and other medical conditions can rob people of their ability to speak. Their communication is limited to the speed at which they can move a cursor with their eyes (just eight to 10 words per minute), in contrast with the natural spoken pace of 120 to 150 words per minute. Now, although still a long way from restoring natural speech, researchers at the University of California, San Francisco, have generated intelligible sentences from the thoughts of people without speech difficulties.

The work provides a proof of principle that it should one day be possible to turn imagined words into understandable, real-time speech circumventing the vocal machinery, Edward Chang, a neurosurgeon at U.C.S.F. and co-author of the study published in April in *Nature*, said in a news conference. "Very few of us have any real idea of what's going on in our mouth when we speak," he said. "The brain translates those thoughts of what you want to say into movements of the vocal tract, and that's what we want to decode."

But Chang cautions that the technology, which has only been tested on people with typical speech, might be much harder to make work in those who cannot speak—and particularly in people who have never been able to speak

because of a movement disorder such as cerebral palsy.

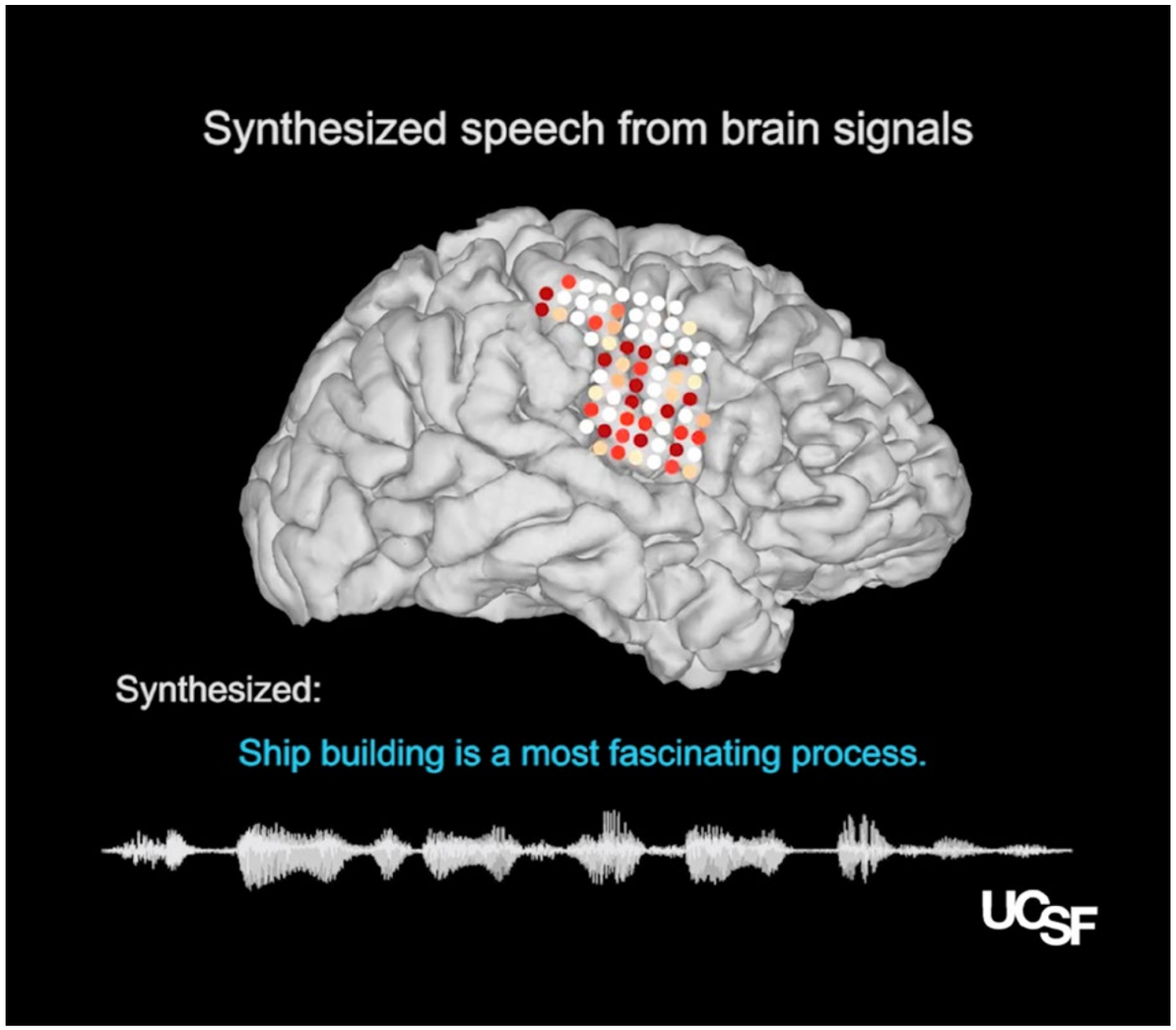
Chang also emphasized that his approach cannot be used to read someone's mind—only to translate words the person wants to say into audible sounds. "Other researchers have tried to look at whether or not it's actually possible to decode essentially just thoughts alone," he says.* "It turns out it's a very difficult and challenging problem. That's only one reason of many that we focus on what people are trying to say."

Chang and his colleagues devised a two-step method for translating thoughts into speech. First, in tests with epilepsy patients whose neural activity was being measured with electrodes on the surface of their brain, the researchers recorded signals from brain areas that control the tongue, lips and throat muscles. Later, using deep-learning computer algorithms trained on naturally spoken words, they translated those movements into audible sentences.

At this point, a decoding system would have to be trained on each person's brain, but the translation into sounds can be generalized across people, said co-author Gopala Anumanchipalli, also of U.C.S.F. "Neural activity is not one-on-one transferable across subjects, but the representations underneath are shareable, and that's what our paper explores," he said.

The researchers asked native English speakers on Amazon's Mechanical Turk crowdsourcing marketplace to transcribe the sentences they heard. The listeners accurately heard the sentences 43 percent of the time when given a set of 25 possible words to choose from, and 21 percent of the time when given 50 words, the study found.

Although the accuracy rate remains low, it would be good enough to make a meaningful difference to a "locked-in" person, who is almost completely paralyzed and unable to speak, the researchers say. "For someone who's locked in and can't communicate at all, a few minor errors would be acceptable," says Marc Slutzky, a neurologist and neural engineer at the Northwestern University Feinberg School of Medicine, who has published related research but was not involved in the new study. "Even a few hundred words would be a huge improvement," he says. "Obviously you'd want to [be able to] say any word you'd want to, but it would still be a lot better than having to type out words one letter at a time, which is the [current] state of the art."



Illustrations of electrode placements on the research participants' neural speech centers, from which activity patterns recorded during speech (*colored dots*) were translated into a computer simulation of the participant's vocal tract (*model, right*), which then could be synthesized to reconstruct the sentence that had been spoken (*sound wave and sentence, below*)

Even when the volunteers did not hear the sentences entirely accurately, the phrases were often similar in meaning to those that were silently spoken. For example, "rabbit" was heard as "rodent," Josh Chartier of

CHANG LAB AND THE UCSF DEPT. OF NEUROSURGERY

U.C.S.F., another co-author of the study, said at the news conference. Sounds like the "sh" in "ship" were decoded particularly well, whereas sounds like "th" in "the" were especially challenging, Chartier added.

Several other research groups in the United States and elsewhere are also making significant advances in decoding speech, but the new study marks the first time that full sentences have been correctly interpreted, according to Slutzky and other scientists not involved in the work.

"I think this paper is an example of the power that can come from thinking about how to harness both the biology and the power of machine learning," says Leigh Hochberg, a neurologist at Massachusetts General Hospital and a neuroscientist at Brown University and Providence VA Medical Center. Hochberg was not involved in the work.

The study is generating excitement in the field, but researchers say the technology is not yet ready for clinical trials. "Within the next 10 years, I think that we'll be seeing systems that will improve people's ability to communicate," says Jaimie Henderson, a professor of neurosurgery at Stanford University, who was not involved in the new study. He says the remaining challenges include determining whether using finer-grained analysis of brain activity will improve speech decoding; developing a device that can be implanted in the brain and can decode speech in real time; and extending the benefits to people who cannot speak at all (whose brains have not been primed to talk).

Hochberg says he is reminded of what is at stake in this kind of research "every time I'm in the neurointensive care unit and I see somebody who may have been walking and talking without difficulty yesterday, but who had a stroke and now can no longer can either move or speak." Although he would love for the work to move faster, Hochberg says he is pleased with the field's progress. "I think brain-computer interfaces will have a lot of opportunity to help people, and hopefully, to help people quickly."

—Karen Weintraub

**Editor's Note (April 24, 2019): This quote has been updated. Chang clarified his original statement to specify that his lab has not attempted to decode thoughts alone.*

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Do Microdoses of LSD Change Your Mind?

A rigorous study has intriguing results

YOU'VE PROBABLY HEARD about microdosing, the "productivity hack" popular among Silicon Valley engineers and business leaders. Microdosers take regular small doses of LSD or magic mushrooms. At these doses, they don't experience mind-bending, hallucinatory trips, but they say they get a jolt in creativity and focus that can elevate work performance, help relationships, and generally improve a stressful and demanding daily life. If its proponents are to be believed, microdosing offers the cure for an era dominated by digital distractions and existential anxiety—a cup of coffee with a little Tony Robbins stirred in.

So far, though, it's been impossible to separate truth from hype. That's because, until recently, microdoses haven't been tested in placebo-controlled trials. Late last year, the first placebo-controlled microdose trial was published. The study concluded that microdoses of LSD appreciably altered subjects' sense of time,

allowing them to more accurately reproduce lapsed spans of time. While it doesn't prove that microdoses act as a novel cognitive enhancer, the study starts to piece together a compelling story on how LSD alters the brain's perceptive and cognitive systems in a way that could lead to more creativity and focus.

The idea behind microdosing traces its roots back decades. In the 1950s, a handful of psychedelic therapists at a mental health facility in Saskatchewan wanted to help alcoholics get clean. They guided the patients through a high-dose, ego-dissolving, LSD experience. When they came out the other side, over half of the patients reported complete recovery from alcoholism. The Canadian government was intrigued and ordered more rigorous trials, this time with placebo controls, and without the experienced "trip guides" offering suggestions on what patients should feel. These trials were a bust. In the fallout, many viewed psychedelic therapy as more shamanism than science. The mindset of the user and suggestion from the therapist (termed "set and setting" to LSD proponents) are just as important as the drug itself. In other words, LSD's effects had as much to do with goings on outside the brain as inside it. To LSD proponents, though, this was part of how it worked. "Set and setting" guard against a bad trip (with large doses), and give the user an idea of what they should experience.

Microdosing is born from this "set and setting" school of psychedelic therapy and one of its intellectual progeny, James Fadiman. The Stanford-trained Fadiman has worked with psychedelics for decades and runs a kind of cottage industry around espousing their powers. In his 2011 book The Psychedelic Explorer's Guide and at a conference talk that same year, Fadiman laid out the concept of microdosing. To microdose, one was to take a dose roughly one tenth of a trip-inducing dose (10 micrograms of LSD) every three or four days, and go about his or her daily life.

Most of what's known about the benefits of microdosing comes from self-reports Fadiman collected (and continues to collect) where microdosers described how the practice transformed their lives. In them, microdosers speak of anxiety and depression melting away, and feelings of determination and self-resolve that helped them achieve professional success. Some color-blind men even saw color for the first time.

The self-reporting experiment doesn't involve placebos or self-blinding, where participants hide dosage information from themselves, and thus is extremely susceptible to observer-expectancy bias. For his part, Fadiman admits that what he does is more "search" than research. But it's quite clear that a prospective microdoser gets expectancy bias (or the right "set and setting" depending on who you ask) from online journalism, Reddit (r/microdosing has close to 50,000 subscribers), or even a consultant. This makes the phenomenon of microdosing more similar to the fringy 1950s Saskatchewan studies than the serious-minded psychedelic research that's sprung up parallel to it.

The phenomenon has gotten so much attention, though, and the claims are so intriguing, that some scientists are attempting to test them with some rigor. A group of psychologists at Goldsmiths, University of London, led by Devin Terhune, published the first placebo-controlled study on microdosing in late 2018. Terhune recruited volunteers who hadn't used LSD in the preceding five years and randomly assigned them into placebo or LSD microdose groups.

Terhune first addressed a simple, but actually elusive, question: are you supposed to feel a microdose of LSD? Many online resources describe microdoses as "subperceptual." In other words, no, you're not supposed to feel the drug take effect. This makes LSD microdoses closer to an antidepressant like Prozac than a truly psychoactive substance like caffeine or marijuana. Others argue that, no, you should feel the microdose, and if you don't, it's not working. As part of a questionnaire, subjects were asked the simple question, "Do you feel the drug?" Interestingly, Terhune found no statistical difference in responses to that question between the placebo and LSD groups. Though this study was limited in scale, it argues that, no, you're not actually feeling anything when you microdose.

But does a microdose change brain function in a subperceptual way? There's a myriad of ways to test this, but Terhune looked specifically at the way the subjects perceive time. When shown a blue dot on a screen for a

specific length of time, the subjects were asked to recreate that length of time by pressing a key. Typically, with longer time intervals, people underrepresent time (that is, hold the key down for a shorter period of time than reality). In the study, those who received microdoses held the key longer, better representing the actual time interval.

Does this mean microdosing makes you smarter? Terhune and his co-authors were cautious in overinterpreting their finding. For one, it's not clear that perceiving time more accurately is preferable. The brain seems to favor underrepresenting time for reasons that are unclear. Disrupting the brain's default way of representing time, though, may beneficial in certain daily tasks or creative pursuits. That's not clear yet, and the relationship between time perception and cognitive function needs to be further developed. Importantly, though, the finding does show that microdoses changed brain function in some way, despite not inducing a strong drug "feeling."

As Terhune and others start testing the meatier microdosing claims with rigorous methods, the era of psychedelic research that James Fadiman had a hand in creating is closing. Organizations that fund psychedelic research are showing more interest in testing microdoses alongside placebo controls. One study, according to its Web site, will test "the short-term effects of various sizes of LSD microdose on creativity, cognitive flexibility and well-being" and "brain activity, cognitive functions and mood" over a four-week period.

So what's riding on these studies? For those who are already convinced of microdosing's powers, probably not much. But quite a lot is at stake for our broader understanding of the brain and the potential for drugs—LSD or otherwise—to enhance cognitive abilities. Unlike large doses of psychedelics, microdoses don't dissolve your ego. You don't become a better version of yourself by falling apart and coming back together, like the Saskatchewan alcoholics. Instead, the mythology around microdosing tells a different, and perhaps even more compelling, story. Through straightforward pharmacology, microdoses may activate just the right amount of receptors for us to be our better selves.

—Sam Rose

KATARZYNA BIALASIEWICZ *GETTY IMAGES*

Infections and Drugs to Treat Them Tied to Eating Disorders in Teens

A new study adds to growing evidence that immune system dysfunction and altered gut microbes may contribute to the development of eating disorders

WHEN Cynthia Bulik started studying eating disorders back in the early 1980s, what she read in the scientific literature clashed with what she saw in the clinic. At the time, theories about the causes of these conditions were focused primarily on explanations based on family dynamics and sociocultural factors.

These descriptions could not explain how, despite dangerously low body weights, patients with eating

disorders were often "hyperactive and said they felt well, and only started feeling poorly when we nourished them," says Bulik, who is currently a professor at both the University of North Carolina and the Karolinska Institute in Sweden. "I became convinced that there had to be something biological going on."

Since then, a growing body of research has confirmed Bulik's observations. Cases of individuals developing rapid alterations in eating behaviors after various infections—the first of which emerged nearly a century ago—have built up over decades. For example, symptoms of eating disorders often occur in pediatric acute-onset neuropsychiatric syndrome (PANS), a condition in which children experience sudden behavioral changes, typically after a streptococcal infection. In addition, over the last few years, several large-scale epidemiological investigations based on data from population registers in Scandinavia—compiled by Bulik and others—have linked eating disorders and autoimmune diseases, including Crohn's, celiac and type 1 diabetes.

Now, Bulik and her colleagues have tied exposure to infections during childhood to an increased risk of developing eating disorders in a large, population-based examination. In their study, which was published in April in *JAMA Psychiatry*, the researchers examined a cohort of 525,643 adolescent girls born in Denmark between 1989 and 2006, among whom 4,240 were diagnosed with an eating disorder. (Boys were excluded from the study because too few males received an eating disorder diagnosis to conduct a meaningful analysis.)

The team's investigation, which included data up until the end of 2012, revealed that girls who were hospitalized for a severe infection had a 22 percent increased risk for anorexia, a 35 percent higher risk for bulimia, and a 39 percent increased risk for other nonspecified eating disorders, compared to those who did not receive a diagnosis. Treatment with anti-infective agents, such as antibiotics or antivirals, also appeared to have an effect: individuals who had received three or more prescriptions for those drugs had a higher risk of developing an eating disorder than those with fewer prescriptions. The risk was greatest within the first three months after a hospital admission or a redeemed prescription.

"[This is] an interesting study that adds to the existing body of literature demonstrating the importance of biological factors in the etiology of eating disorders," says Neville Golden, a professor of pediatrics at Stanford University who was not involved in this work. Although these findings can only establish a correlation between infections and eating disorders without proving a causal link, the authors contend that their results support the hypothesis that the immune system might be a culprit. The idea also receives support from other observations, such as the previously established connections between these conditions and autoimmune disorders and reports of elevated levels of cytokines, molecules involved in inflammation, in patients with anorexia.

Another potential explanation for the latest findings, according to study co-author Lauren Breithaupt, a clinical and research fellow at Harvard Medical School, is that perturbations in the gut microbiome may be responsible for the observed changes in behavior. "We know that both contracting an infection and taking an anti-infective agent alters the stability of microbes in our gut," Breithaupt explains. "And the connection between the gut and the brain, the gut-brain axis, is really strong—so the changes that occur could affect behaviors via this communication line."

Bulik and her colleagues have identified evidence that eating disorders can alter the gut microbiome. In a 2015 study, they reported that people with anorexia nervosa had a significantly less varied population of intestinal microbes than healthy individuals, and a normal level of diversity was only partially restored after treatment. One ongoing hypothesis, according to Bulik, is that the bacteria that survive in anorexia nervosa are the ones that thrive in a nutrient- and energy-poor environment.

If this were indeed the case, one fascinating possibility would be that the presence of those microbes could lead to a self-sustaining problem—since those newly dominant bugs might be at risk when patients return to a healthy diet. "We know that after you renourish someone with anorexia nervosa in the hospital, a very common thing that happens is we send them back home and they lose weight again," Bulik says. "There has

always been a psychological explanation for that … but what if that somehow is the survival of the bacterial fittest?"

This is one of several theories about how the microbiome might contribute to eating disorders. There are also ideas about how microbes might influence inflammation, according to Beate Herpertz-Dahlmann, a child and adolescent psychiatrist at the RWTH University Clinics in Germany who is currently involved in projects that are investigating this link in several European countries.

Bacteria, for instance, may develop antibodies against molecules that influence appetite. Another possibility is that a deeply altered microbiome could lead to a so-called leaky gut, in which pathological material seeps through the intestines into the blood vessels, evoking an immune response elsewhere in the body, in areas such as the brain.

"[Eating disorders] were first described in the 1600s, and it's amazing how little we know about how to manage and treat them," Golden says. "A better understanding of how these diseases develop will advance us in our treatments."

—Diana Kwon

The Adult Brain Does Grow New Neurons After All, Study Says

Study points toward lifelong neuron formation in the human brain's hippocampus, with implications for memory and disease

IF THE MEMORY center of the human brain can grow new cells, it might help people recover from depression and post-traumatic stress disorder (PTSD), delay the onset of Alzheimer's, deepen our understanding of epilepsy and offer new insights into memory and learning. If not, well then, it's just one other way people are different from rodents and birds.

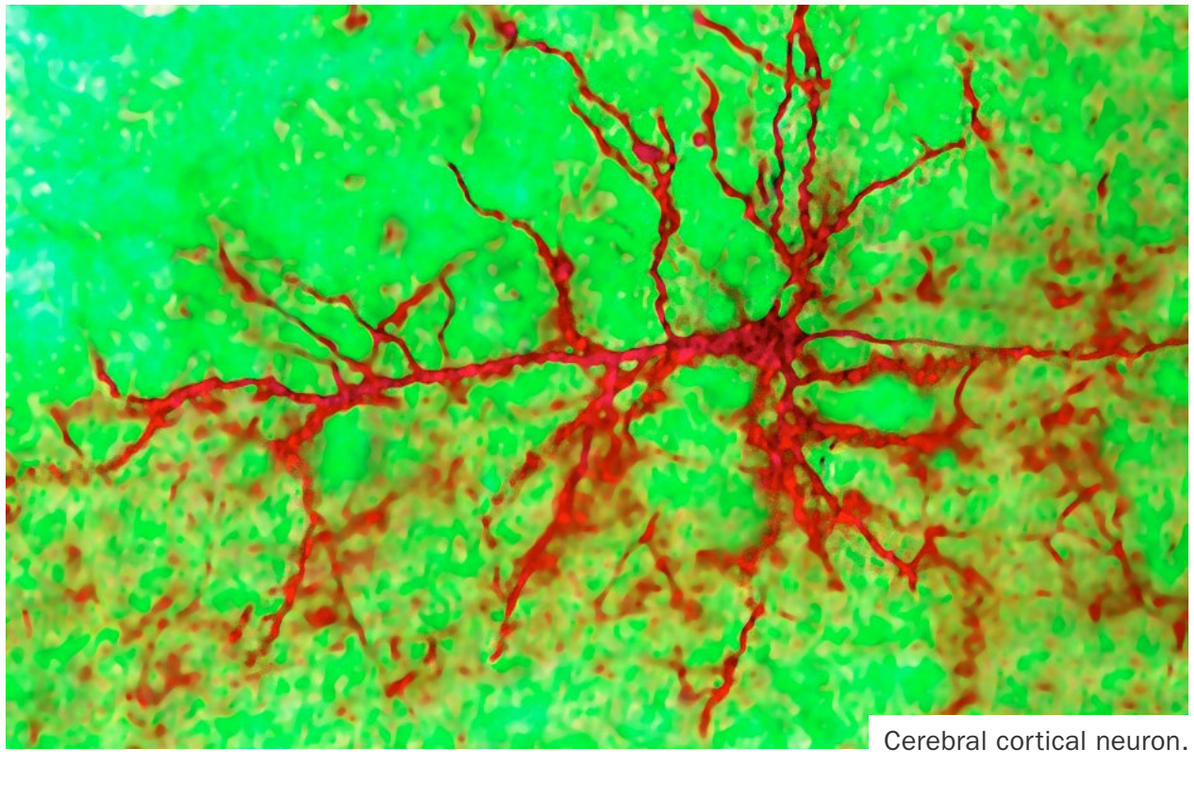
For decades, scientists have debated whether the birth of new neurons—called neurogenesis—was possible in an area of the brain that is responsible for learning, memory and mood regulation. A growing body of research suggested they could, but then a *Nature* paper last year raised doubts.

Now, a new study published in March in another of the *Nature* family of journals—*Nature Medicine*—tips the balance back toward "yes." In light of the new study, "I would say that there is an overwhelming case for the neurogenesis throughout life in humans," Jonas Frisén, a professor at the Karolinska Institute in Sweden, said in an e-mail. Frisén, who was not involved in the new research, wrote a News and Views about the study in the March issue of *Nature Medicine*.

Not everyone was convinced. Arturo Alvarez-Buylla was the senior author on last year's *Nature* paper, which questioned the existence of neurogenesis. Alvarez-Buylla, a professor of neurological surgery at the University of California, San Francisco, says he still doubts that new neurons develop in the brain's hippocampus after toddlerhood.

"I don't think this at all settles things out," he says. "I've been studying adult neurogenesis all my life. I wish I could find a place [in humans] where it does happen convincingly."

For decades, some researchers have thought that the brain circuits of primates—including humans—would be too disrupted by the growth of substantial numbers of new neurons. Alvarez-Buylla says he thinks the scientific debate over the existence of neurogenesis should continue. "Basic knowledge is fundamental.



Cerebral cortical neuron.

GETTY IMAGES

Just knowing whether adult neurons get replaced is a fascinating basic problem," he says.

New technologies that can locate cells in the living brain and measure the cells' individual activity, none of which were used in the *Nature Medicine* study, may eventually put to rest any lingering questions.

A number of researchers praised the new study as thoughtful and carefully conducted. It's a "technical tour de force," and addresses the concerns raised by last year's paper, says Michael Bonaguidi, an assistant professor at the University of Southern California Keck School of Medicine.

The researchers, from Spain, tested a variety of methods of preserving brain tissue from 58 newly deceased people. They found that different methods of preservation led to different conclusions about whether new neurons could develop in the adult and aging brain.

Brain tissue has to be preserved within a few hours after death, and specific chemicals used to preserve the tissue, or the proteins that identify newly developing cells will be destroyed, said María Llorens-Martín, the paper's senior author. Other researchers have missed the presence of these cells, because their brain tissue was not as precisely preserved, says Llorens-Martín, a neuroscientist at the Autonomous University of Madrid in Spain.

Jenny Hsieh, a professor at the University of Texas San Antonio who was not involved in the new research, said the study provides a lesson for all scientists who rely on the generosity of brain donations. "If and when we go and look at something in human postmortem, we have to be very cautious about these technical issues."

Llorens-Martín said she began carefully collecting and preserving brain samples in 2010, when she realized that many brains stored in brain banks were not adequately preserved for this kind of research. In their study, she and her colleagues examined the brains of people who died with their memories intact, and those who died at different stages of Alzheimer's disease. She found that the brains of people with Alzheimer's showed few if any signs of new neurons in the hippocampus—with less signal the further along the people were in the course of the disease. This suggests that the loss of new neurons—if it could be detected in the living brain—would be an early indicator of the onset of Alzheimer's, and that promoting new neuronal growth could delay or prevent the disease that now affects more than 5.5 million Americans.

"I don't think this at all settles things out. I've been studying adult neurogenesis all my life. I wish I could find a place [in humans] where it does happen convincingly."

—Arturo Alvarez-Buylla

Rusty Gage, president of the Salk Institute for Biological Studies and a neuroscientist and professor there, says he was impressed by the researchers' attention to detail. "Methodologically, it sets the bar for future studies," says Gage, who was not involved in the new research but was the senior author in 1998 of a paper that found the first evidence for neurogenesis. Gage says this new study addresses the concerns raised by Alvarez-Buylla's research. "From my view, this puts to rest that one blip that occurred," he says. "This paper in a very nice way … systematically evaluates all the issues that we all feel are very important."

Neurogenesis in the hippocampus matters, Gage says, because evidence in animals shows that it is essential for pattern separation, "allowing an animal to distinguish between two events that are closely associated with each other." In people, Gage says, the inability to distinguish between two similar events could explain why patients with PTSD keep reliving the same experiences, even though their circumstances have changed. Also, many deficits seen in the early stages of cognitive decline are similar to those seen in animals whose neurogenesis has been halted, he says.

In healthy animals, neurogenesis promotes resilience in stressful situations, Gage says. Mood disorders, including depression, have also

been linked to neurogenesis.

Hsieh says her research on epilepsy has found that newborn neurons get miswired, disrupting brain circuits and causing seizures and potential memory loss. In rodents with epilepsy, if researchers prevent the abnormal growth of new neurons, they prevent seizures, Hsieh says, giving her hope that something similar could someday help human patients. Epilepsy increases someone's risk of Alzheimer's as well as depression and anxiety, she says. "So, it's all connected somehow. We believe that the new neurons play a vital role connecting all of these pieces," Hsieh says.

In mice and rats, researchers can stimulate the growth of new neurons by getting the rodents to exercise more or by providing them with environments that are more cognitively or socially stimulating, Llorens-Martín says. "This could not be applied to advanced stages of Alzheimer's disease. But if we could act at earlier stages where mobility is not yet compromised," she says, "who knows, maybe we could slow down or prevent some of the loss of plasticity [in the brain]."

—Karen Weintraub

How We Roll: Study Shows We're More Lone Wolves Than Team Players

Results may explain why collective action on climate change and health policy is so difficult

STEVE SMITH *GETTY IMAGES*

WHAT CREDO WOULD you choose: "Share and share alike?" or "To each his own"? The choice doesn't relate only to material goods or socialism versus capitalism. It can also reflect attitudes about how we solve our collective problems, such as affordable access to health care or threats from climate change. Despite the existence of shared resources in our lives—water, air, land, tax dollars—some people will lean into a go-it-alone approach, with each individual deciding for themselves what's best. Others will look to group decision-making. What's the tipping point for shifting from maverick to team player?

Researchers at Leiden University, the Netherlands, addressed that question using a computer game in which students had to decide whether to use a set of virtual resources to solve a problem individually or collectively. The investigators found that these study participants had a "remarkable tendency" to waste resources for the sake of an independent solution rather than efficiently using what in the social sciences is referred to as "the commons." The study results were published April 17 in *Science Advances.*

The choice to follow the loner track even if it means wasted resources probably sounds familiar. Such useless waste, a "tragedy of the commons," as the authors call it, is one that societies face in all kinds of situations. Study author Jörg Gross,

assistant professor at Leiden University's Institute of Psychology, cites several examples of real-world problems from modern life that inspired the study, including use of public versus private transportation. After all, almost everyone needs to get from Location A to Location B. Rather than create universal public transit solutions, though, people more often turn to using private vehicles.

The cultural aspect of these findings stands out, says Michael Varnum, assistant professor of psychology at Arizona State University, who was not involved in the study. "That these students live in the Netherlands is interesting," he says, because Dutch society has a solid social safety net with good infrastructure, public health care and education. "I would guess that the effects observed in the present studies might be more pronounced in societies that have greater levels of income inequality and less generous public benefits, such as the U.S."

To observe these effects, Gross and co-author Carsten K. W. De Dreu, who is affiliated with both Leiden University and the University of Amsterdam, split up 160 participants into 40 groups of four people each. The groups faced a simulated problem that they could solve by committing sufficient resources to it individually or as a community. Participants, each given 100 resource points to start, could put their virtual resources into either a personal pool or a shared pool.

After each round of play, the players could scrutinize what had accumulated in the community and their personal pools and how much others in their group had given up in each round. By a final round, the four players in each group had to have accumulated 160 points in the community pool. If the group failed to meet that goal, each individual had to have an accumulation of 40, 50, 60, 70 or 80 points (the researchers varied the individual requirement across games). If the group built up 160 points in the community pool, everyone got to keep the individual resources they had left. If the group didn't achieve the 160 points, whoever failed to meet the personal target set for the game (60 points, for example) also lost everything else.

With four players per group, the most obvious and equitable solution to meeting the 160-point goal was to pony up 40 of the 100 individually allocated resource points to the community pot, keeping the rest (60 points) for themselves. Everyone wins something and keeps something (60 points), and no one loses everything.

I would guess that the effects observed in the present studies might be more pronounced in societies that have greater levels of income inequality and less generous public benefits, such as the U.S."

—Michael Varnum

But if a player chose the individual route, all possible scenarios (40, 50, 60, 70 or 80 points) cost them as much or more than a contribution of 40 points to the community pot. For example, if the individual requirement for reaching the solution was 60 points, the player opting for that choice would retain only 40 of the player's original 100 points. If the player instead chose to give 40 resource points to the community pot, that player would keep 60 points, a 20-point improvement—as long as the community pool still added up to 160 points.

The peak cost for an individual solution was 80 of the 100 resource points available to each player, double the 40 per person needed for the community option. Yet even at that rate, 15 percent of players remained diehard individualists. They were willing to give up 80 points to "solve" a problem individually rather than risk contributing 40 to a community pool—and see other group members investing in the community pool possibly lose everything. These individualist behaviors left each group wasting an average of 45 resource points per game, more than a quarter of the 160 that they needed to collec-

tively "solve" the problem.

Four categories of decision-makers emerged. There were the altruists, who invested more than their fair share. The cooperators readily ponied up their 40 points to the collective. Individualists stuck to their guns, preferring to pay the individual amount rather than contribute to a collective. And then there were the free riders. They invested less than their share of at least 40 points in the collective pool (perhaps keeping 70 or 80 points for themselves) but still reaped benefits from altruists making up the difference, which Gross describes as an "optimal strategy" (economically speaking) for an individual. He gives cutting carbon dioxide emissions as an example: a free rider who personally takes few steps to limit carbon dioxide emissions will still benefit when others make great efforts to do so.

In such a situation, peer pressure might be expected to operate most on the free-riding slackers, but that's not what happened. In one set of games, Gross and De Dreu allowed players to punish each other by dinging them with up to five "peer punishments." Each punishment decreased the take for the punisher by one reward point but cost the punished peer three points.

The free riders might seem like the obvious targets for this peer punishment, but they weren't. Instead, the "punishment" turned into an expensive feuding between the altruists, who meted out the most punishments, and individualists, whom the altruists targeted. Meanwhile, the free riders and those who stuck to contributing only their fair share hung back. The feuding increased costs for the collective as a whole, which the authors say calls into question how effective unfettered peer punishment is in real life.

The peer pressure worked on individualists, though, Gross says. "Peer punishment 'forced' them into cooperation, but they were less willing to enforce cooperation in others," he says, with the result that free riders still continued without paying their fair share.

Varnum says such an outcome needs consideration in the context of earlier findings showing culture-based differences in the effects of peer punishment. These earlier results showed that in a collectivist society with a default expectation of community participation, punishment reduces free-rider behavior. In individualistic cultures, however, punishment does not influence freeloading behaviors. Varnum says that a future study might investigate how the same study methods would play out in societies that are largely collectivist, such as India, China or Japan as opposed to the Netherlands.

—Emily Willingham

In Search of a (Subjective) Fountain of Youth

Research finds a fascinating connection between IQ and aging

By David Z. Hambrick

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David Z. Hambrick is a professor in the department of psychology at Michigan State University and director of the MSU Expertise Lab. His research focuses on expertise and intelligence.

AS YOU MAY HAVE NOTICED AT YOUR LAST HIGH school reunion, some people age more gracefully than others. Jean Calment, who died in 1997 at the age of 122 and is the world record holder for longest human lifespan, is reported to have stayed mentally sharp her entire life. She took up fencing at 85 and rode a bike until she was 100. At the other extreme, people with early-onset Alzheimer's may begin experiencing cognitive deficits in their 30s.

People also differ in subjective age—how old they feel. Older adults who report feeling younger than their years tend to be mentally and physically healthier than people who report feeling older. According to one popular view, aging is a "state of mind" that is directly under a person's control. However, a new study published in the journal *Intelligence* reveals that the developmental processes that influence subjective age actually begin early in life. People who scored high on an IQ test in their late teens felt younger once they reached their 70s than people who scored lower on the IQ test.

The data were from the Wisconsin Longitudinal Study (or WLS), which has followed a random sample of 10,317 people born between 1937 and 1940. The participants took an intelligence test in 1957, when they were seniors in high school, while data on education, health and personality were collected in the early 1990s. Then, in 2011, the participants were asked how old they felt most of the time. For each person, the researchers computed an index of subjective age by subtracting this value ("felt age") from chronological age and dividing the difference by chronological age. Thus, people with a negative score felt older than they actually were, whereas people with a positive score felt younger.

On average, the people in the study felt 17 percent younger than their chronological age. For example, a person who was 70 years old reported feeling like they were only 58. However, the difference between chronological age and subjective age varied by intelligence, as assessed by the IQ test given more than 50 years earlier. The people with the highest IQs reported feeling the youngest.

IQ correlates with any number of factors that could explain this correlation, including education. People who score high on intelligence tests are generally more educated than people who score lower. (The correlation between IQ and educational achievement is among the highest correlations observed in psychological research.) In turn, highly educated people secure better paying and less physically strenuous jobs than less educated people and can afford things that might keep them feeling young, from good health care to luxury vacations.

As plausible as this explanation seems, statistical analyses revealed that the relationship between IQ and subjective age was explained not by education but by a personality trait: openness to experience. A person high in openness to experience is intellectually curious, independent and imaginative; they prefer variety over routine and enjoy learning and trying new things. Once the researchers statistically controlled for openness to experience, the relationship between IQ and subjective age vanished.

The study helps us understand the relationship between psychological traits measured early life and the aging process. As now documented in large-sample studies from around the world, intelligence predicts longevity: People with high IQs tend to live longer than people with lower IQs. One reason this may be the case is that intelligence tests, in addition to measuring cognitive functioning that bears on people's ability to make decisions conducive to living a long and healthy life, may capture information about people's personalities. People who are high in openness to experience may be more likely to seek out information that can be beneficial to their health. Staying abreast of changes in the world, they may also feel more vital than people lower in openness to experience.

The study also opens avenues of applied research on aging. Both intelligence and personality are relatively stable psychological traits and are not easily changed through intervention. However, interventions that target specific behaviors such as exercising, eating healthy, and becoming civically engaged can improve people's physical and psychological well-being. One possible consequence of these interventions is that people may begin to feel younger than their years. There may be no fountain of youth, but this type of intervention may at least soften people's experience of growing older.

Behind the Buzz: How Ketamine Changes the Depressed Patient's Brain

The anesthetic-cum-party-drug restores the ability to make connections among brain cells

By Simon Makin

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Simon Makin is a freelance science writer based in London.

THE FOOD AND DRUG Administration's approval in March of a depression treatment based on ketamine generated headlines, in part, because the drug represents a completely new approach for dealing with a condition the World Health Organization has labeled the leading cause of disability worldwide. The FDA's approval marks the first genuinely new type of psychiatric drug—for any condition—to be brought to market in more than 30 years.

Although better known as a party drug, the anesthetic ketamine has spurred excitement in psychiatry for almost 20 years, since researchers first showed that it alleviated depression in a matter of hours. The rapid reversal of symptoms contrasted sharply with the existing set of antidepressants, which take weeks to begin working. Subsequent studies have shown ketamine works for patients who have failed to respond to multiple other treatments, and so are deemed "treatment-resistant."

Despite this excitement, researchers still don't know exactly how ketamine exerts its effects. A leading theory proposes that it stimulates regrowth of synapses (connections between neurons), effectively rewiring the brain. Researchers have seen these effects in animals' brains, but the exact details and timing are elusive.

A new study, from a team led by neuroscientist and psychiatrist Conor Liston at Weill Cornell Medicine, has confirmed that synapse growth is involved, but not in the way many researchers were expecting. Using cutting-edge technology to visualize and manipulate the brains of stressed mice, the study reveals how ketamine first induces changes in brain circuit function, improving "depressed" mice's behavior within three hours, and only later stimulating regrowth of synapses.

As well as shedding new light on the biology underlying depression, the work suggests new avenues for exploring how to sustain antidepressant effects over the long term. "It's a remarkable engineering feat, where they were able to visualize changes in neural circuits over time, corresponding with behavioral effects of ketamine," says Carlos Zarate, chief of the Experimental Therapeutics and Pathophysiology Branch at the National Institute of Mental Health, who was not involved in the study. "This work will likely set a path for what treatments should be doing before we move them into the clinic."

Another reason ketamine has researchers excited is that it works differently than existing antidepressants. Rather than affecting one of the "monoamine" neurotransmitters (serotonin, norepinephrine and dopamine), as standard antidepressants do, it acts on glutamate, the most common chemical messenger in the brain. Glutamate plays an important role in the changes synapses undergo in response to experiences that underlie learning and memory. That is why researchers suspected such "neuroplasticity" would lie at the heart of ketamine's antidepressant effects.

Ketamine's main drawback is its side effects, which include out-of-body experiences, addiction and bladder problems. It is also not a "cure." The majority of recipients who have severe, difficult-to-treat depression will ultimately relapse. A course of multiple doses typically wears off within a few weeks to months. Little is known about the biology underlying depressive states, remission and relapse. "A big question in the field concerns the mechanisms that mediate transitions between depression states over time," Liston says. "We were trying to get a better handle on that in the hopes we might be able to figure out better ways of preventing depression and sustaining recovery."

Chronic stress depletes synapses in certain brain regions, notably the medial prefrontal cortex (mPFC), an area implicated in multiple aspects of depression. Mice subjected to stress display depressionlike behaviors, and with antidepressant treatment, they often improve. In the new study, the researchers used light microscopes to observe tiny structures called spines located on dendrites (a neuron's "input" wires) in the mPFC of stressed mice. Spines play a key role because they form synapses if they survive for more than a few days.

For the experiment, some mice became stressed when repeatedly restrained; others became so after they were administered the stress hormone corticosterone. "That's a strength of this study," says neuroscientist Anna Beyeler,

of the University of Bordeaux, France, who was not involved in the work, but wrote an accompanying commentary article in *Science*. "If you're able to observe the same effects in two different models, this really strengthens the findings." The team first observed the effects of subjecting mice to stress for 21 days, confirming that this resulted in lost spines. The losses were not random, but clustered on certain dendrite branches, suggesting the damage targets specific brain circuits.

The researchers then looked a day after administering ketamine and found that the number of spines increased. Just over half appeared in the same location as spines that were previously lost, suggesting a partial reversal of stress-induced damage. Depressionlike behaviors caused by the stress also improved. The team measured brain circuit function in the mPFC, also impaired by stress, by calculating the degree to which activity in cells was coordinated, a measure researchers term "functional connectivity." This too improved with ketamine.

When the team looked closely at the timing of all this, they found that improvements in behavior and circuit function both occurred within three hours, but new spines were not seen until 12 to 24 hours after treatment. This suggests that the formation of new synapses is a consequence, rather than cause, of improved circuit function. Yet they also saw that mice who regrew more spines after treatment performed better two to seven days later. "These findings suggest that increased ensemble activity contributes to the rapid effects of ketamine, while increased spine formation contributes to the sustained antidepressant actions of ketamine," says neuroscientist Ronald Duman of the Yale School of Medicine, who was not involved in the study. Although the molecular details of what happens in the first hours are not yet fully understood, it seems a restoration of coordinated circuit activity occurs first; this is then entrenched by neuroplasticity effects in synapses, which then maintain behavioral benefits over time.

"We're slowly identifying specific regions associated with specific behaviors."
—Anna Beyeler

To prove that new synapses were a cause of antidepressant effects, rather than just coinciding with the improved behaviors, the team used a newly developed optogenetic technique, which allowed them to eliminate newly formed spines using light. Optogenetics works by introducing viruses that genetically target cells, causing them to produce light-sensitive proteins. In this case, the protein is expressed in newly formed synapses, and exposure to blue light causes the synapse to collapse. The researchers found that eliminating newly formed synapses in ketamine-treated mice abolished some of the drug's positive effects, two days after treatment, confirming that new synapses are needed to maintain benefits. "Many mechanisms are surely involved in determining why some people relapse and some don't," Liston says, "but we think our work shows that one of those involves the durability of these new synapses that form."

And Liston adds: "Our findings open up new avenues for research, suggesting that interventions aimed at enhancing the survival of these new synapses might be useful for extending ketamine's antidepressant effects." The implication is that targeting newly formed spines might be useful for maintaining remission after ketamine treatment. "This is a great question and one the field has been considering," Duman says. "This could include other drugs that target stabilization of spines, or behavioral therapies designed to engage the new synapses and circuits, thereby strengthening them."

The study used three behavioral tests: one involving exploration, a second a struggle to escape, and a third an assessment of how keen the mice are on a sugar solution. This last test is designed to measure anhedonia—a symptom of depression in which the ability to experience pleasure is lost. This test was unaffected by deleting newly formed spines, suggesting that the formation of new synapses in the mPFC is important for some symptoms, such as apathy, but not others (anhedonia)—and that different aspects of depression involve a variety of brain circuits.

These results could relate to a study published last year that found activity in another brain region, the lateral habenula, is crucially involved in anhedonia, and injecting ketamine directly into this region improves anhedonia-related behavior in mice. "We're slowly identifying specific regions associated with specific behaviors," Beyeler says. "The factors leading to depression might be different depending on the individual, so these different models might provide information regarding the causes of depression."

One caveat is that the study looked at only a single dose, rather than the multiple doses involved in a course of human treatment, Zarate says. After weeks of repeated treatments, might the spines remain, despite a relapse, or might they dwindle, despite the mice still doing well? "Ongoing effects with repeated administration, we don't know," Zarate says. "Some of that work will start taking off now, and we'll learn a lot more." Of course, the main caution is that stressed mice are quite far from humans with depression. "There's no real way to measure synaptic plasticity in people, so it's going to be hard to confirm these findings in humans," Beyeler says.

The Light Triad vs. Dark Triad of Personality

New research contrasts two very different profiles of human nature

By Scott Barry Kaufman

GARY WATERS *GETTY IMAGES*

Scott Barry Kaufman is a psychologist at Columbia University exploring intelligence, creativity, personality and well-being. In addition to writing the column Beautiful Minds for *Scientific American*, he is author and/or editor of eight books, including *Wired to Create: Unravelling the Mysteries of the Creative Mind* (with Carolyn Gregoire) and *Ungifted: Intelligence Redefined*.

"I still believe, in spite of everything, that people are truly good at heart."
–Anne Frank

"What's one less person on the face of the earth, anyway?"
–Ted Bundy

WHY ARE DARK TRIAD PEOPLE SO SEDUCTIVE? Why do they get all the research attention? I asked my colleague David Yaden in his office. Immediately his ears pricked up, and he asked me to send him papers on the dark triad, remarking that he hadn't heard of the dark triad but that it sounded fascinating (thus proving my point).

When I went back to my office, I emailed some papers to David and my colleague Elizabeth Hyde. In a quick email response, David simply wrote back, "light triad"? Now *my* ears pricked up. *Was there such a thing? Had it been studied?*

The dark triad has already been well-studied. First discovered by Delroy Paulhus and Kevin Williams in 2002, the dark triad of personality consists of narcissism (entitled self-importance), Machiavellianism (strategic exploitation and deceit) and psychopathy (callousness and cynicism). While these three traits had traditionally been studied mostly among clinical populations (e.g., criminals), Paulhus and Williams showed that each of these traits is clearly on a continuum—we are all at least a little bit narcissistic, Machiavellian and psychopathic.

Since their initial paper, research on the topic has increased quite a bit each year, with two-thirds of the publications of the dark triad appearing in 2014 and 2015 alone. While each of the members of the dark triad has unique features and correlates, there is enough overlap among these "socially aversive" traits that Paulhus has argued that they "should be studied in concert." Indeed, there does appear to be a "dark core" to personality.

While research on dark personalities has certainly contributed to our understanding of the darker side of human nature, and how each of us differs in the extent to which we consistently exhibit dark patterns of thoughts, feelings and behaviors in our daily lives, what about the light side of human nature?

EVERYDAY SAINTS

Socially aversive people certainly exist, but what about everyday saints? I'm not talking about the person who publicly does a lot of giving, and receives many public accolades and awards for all of their giving (and who constantly gives to others in order to achieve personal success). I'm talking about the person who, just by their being, shines their light in every direction. The person who isn't constantly strategic about their giving, but who emits unconditional love naturally and spontaneously because that's just who they are.

So this is what we set out to find out. Through many email exchanges and personal meetings, David, Elizabeth and I looked at existing tests of the dark triad and brainstormed a variety of items relating to the conceptual opposite characteristics of each member of the dark triad, but we created items that weren't simply the reverse of the dark triad items. Our initial pool of items related to forgiveness, trust, honesty, caring, acceptance, seeing the best in people and getting intrinsic enjoyment from making connections with others instead of using people as a means to an end.

To our surprise (we hadn't expected there to necessarily be three factors), three distinct factors emerged from our studies, which we labeled: Kantianism (treating people as ends unto themselves, not mere means), Humanism (valuing the dignity and worth of each individual) and Faith in Humanity (believing in the fundamental goodness of humans).

After a series of refinements of our initial items (and sophisticated statistical analyses conducted by Eli Tsukayama), we settled on 12 items that capture the essence of this light triad. You can take the Light Triad Scale here (and also receive information on your light vs. dark triad balance).

We have now administered the Light Triad Scale to thousands of people of different ages, genders, races and ethnicities, and the results are far-reaching. First, it is clear that the light triad is not merely the opposite of the

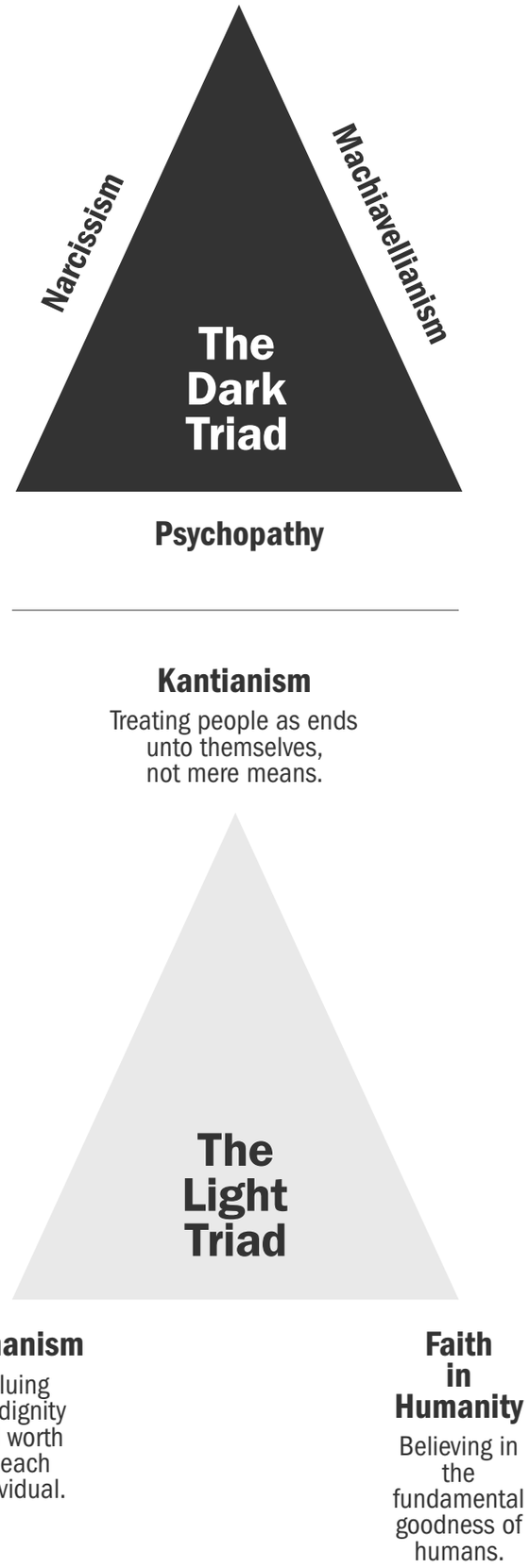
dark triad. While the two are negatively related to each other, the relationship is only moderate in size (a correlation of about 0.50), supporting the idea that there is at least a little bit of light and dark in each of us. In my view, it's best to view those who score extremely high on the dark triad not as a separate species of human (after all, to have a dark side is to be human) but as magnified and unleashed versions of potentialities that lie within all of us.

With that said, it seems like Anne Frank may have been on to something in the opening quote of this article. We calculated a light triad vs. dark triad balance score for each participant by subtracting each person's score on the dark triad from their score on the light triad. The average balance score of the entire sample was 1.3, suggesting that the average person is tipped more toward the light relative to the dark in their everyday patterns of thoughts, behaviors and emotions. As you can see in this scatterplot, extreme malevolence is extremely rare in the general population.

PORTRAITS OF THE LIGHT AND DARK TRIAD

What about the contrasting profiles of the light and dark triad? We found that the dark triad was positively correlated with being younger, being male, being motivated by power, instrumental sex, achievement and affiliation (but not intimacy), having self-enhancement values, immature defense styles, conspicuous consumption, selfishness and viewing their creative work and religious immortality as routes to death transcendence. The dark triad was negatively correlated with life satisfaction, conscientiousness, agreeableness, self-transcendent values, compassion, empathy, a quiet ego, a belief that humans are good and a belief that one's own self is good.

The dark triad also showed positive correlations with a variety of variables that could facilitate one's more agentic-related goals. For instance, the dark triad was



positively correlated with utilitarian moral judgment and the strengths of creativity, bravery and leadership, as well as assertiveness, in addition to motives for power, achievement and self-enhancement. Also, an unexpected correlation between the dark triad and curiosity was found, which was localized primarily to the embracing ("I like to do things that are a little frightening," "I prefer jobs that are excitingly unpredictable") and deprivation ("It disturbs me when I don't understand a solution," "It bothers me if I don't know a word") forms of curiosity.

Interestingly, after we controlled for the more antagonistic elements of the dark triad, the dark triad actually showed positive associations with a number of growth-oriented outcomes. These findings suggest that the callous and manipulative core of the dark triad does not do these individuals many favors. It's likely that the variance that is left over once the malevolence-related variance of the dark triad is removed is associated with agentic extraversion (the aspect of extraversion associated with assertiveness, which may provide a protective factor for those scoring higher on the dark triad*).

In stark contrast, the overall picture provided by the pattern of correlations with the light triad was quite different than the dark triad. The light triad was associated with being older, being female, less childhood unpredictability, as well as higher levels of religiosity, spirituality, life satisfaction, acceptance of others, belief that others are good, belief that one's self is good, compassion, empathy, openness to experience, conscientiousness, positive enthusiasm, having a quiet ego and a belief that one can live on through nature and biosociality (having children) after one's personal death.

Individuals scoring higher on the Light Triad Scale also reported more satisfaction with their relationships, competence and autonomy, and they also reported higher levels of secure attachment style and eros in their relationships. In general, the light triad was related to being pri-

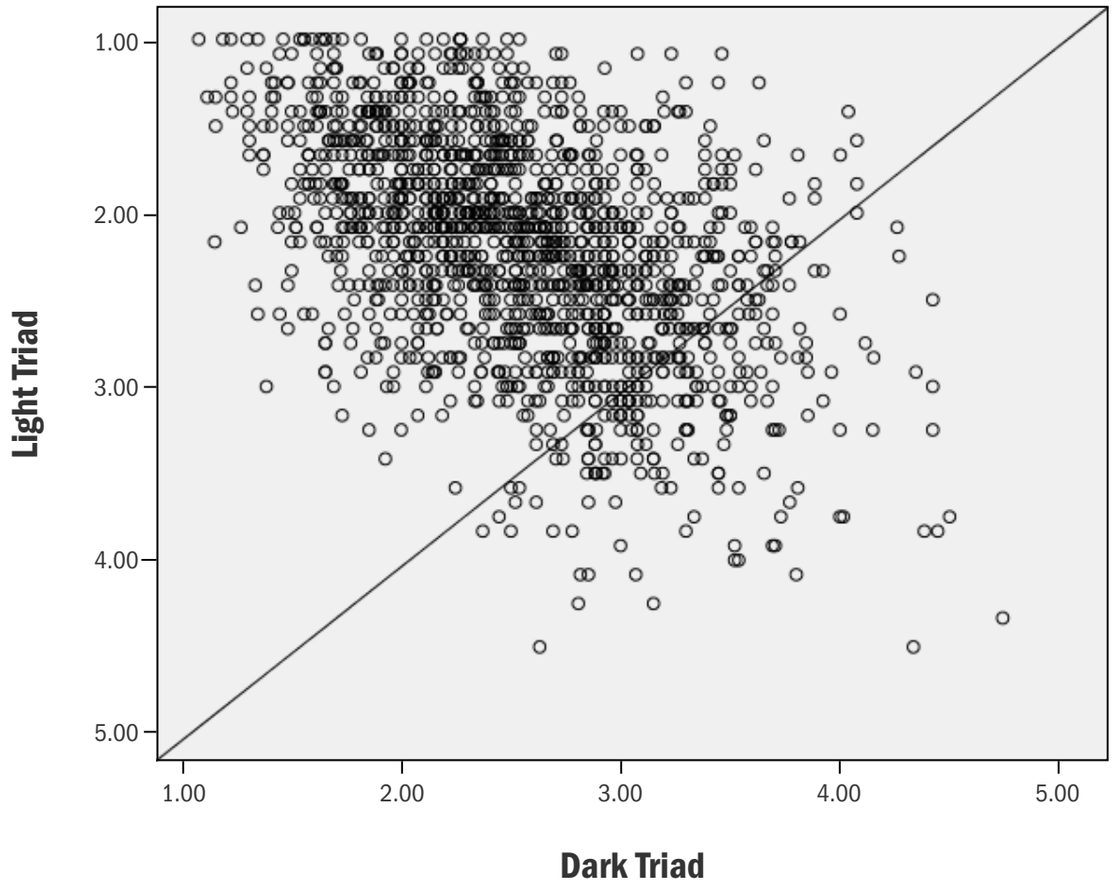
marily motivated by intimacy and self-transcendent values. Many character strengths correlated with the light triad, including curiosity, perspective, zest, love, kindness, teamwork, forgiveness and gratitude.

Note that the flavor of curiosity associated with light triad—stretching ("I actively seek as much information as I can in new situations," "I view challenging situations as an opportunity to grow and learn")—differed from the flavor of curiosity associated with the dark triad (primarily embracing and deprivation). Mature defense styles were also associated with the light triad (e.g., humor, sublimation, altruism, anticipation), as were optimistic beliefs about the self, the world and one's future. Individuals scoring higher on the Light Triad Scale also reported higher self-esteem, authenticity and a stronger sense of self.

In general, the light triad does not appear to be associated with any obvious downsides, with a few possible exceptions depending on the context. The light triad was negatively correlated with the motives for achievement and self-enhancement (even though the light triad was positively related to productivity and competence). In terms of character strengths, unlike the dark triad, the light triad was uncorrelated with bravery or assertiveness. Such characteristics may be important for reaching one's more challenging goals and fully self-actualizing.

Additionally, in line with our predictions, the light triad was related to greater interpersonal guilt—including survivor ("I sometimes feel I don't deserve the happiness I achieved"), separation ("It makes me anxious to be away from home for too long") and omnipotent responsibility ("I worry a lot about the people I love even when they seem to be fine") forms of guilt. While it may be adaptive to experience these forms of interpersonal guilt for facilitating relationships and repairing damage in a relationship, these forms of guilt may limit one's ambitions for fear of succeeding while others remain less successful.

The light triad was also correlated with greater "reaction formation," which is considered by some psychologists as a neurotic defense style (but which I conceptualize in my own work as an aspect of mature altruism). The reaction formation scale consisted of the following items: "If someone mugged me and stole my money, I'd rather he be helped than punished" and "I often find myself being very nice to people who by all rights I should be angry at." While having such "loving kindness" even for one's enemies is conducive to one's own well-being, these attitudes, coupled with greater interpersonal guilt, could make those scoring higher on the light triad potentially more open to exploitation and emotional manipulation from those scoring higher on the dark triad. Indeed, we believe further investigation of the social interactions between extreme light vs. dark triad scorers would be an interesting future line of research.



CONCLUSION

There are definitely limitations of our studies, and lots of areas for future research extending and developing our work. The 12-item Light Triad Scale should be viewed as a first draft, and our four studies should be seen as more exploratory than definitive.

Nevertheless, we hope our research helps balance the force in personality psychology. Yes, everyday psychopaths exist. But so do everyday saints, and they are just as worthy of research attention and cultivation in a society that sometimes forgets that not only is there goodness in the world, but there is also goodness in each of us as well.

You can read our scientific paper here. Also, you can take the Light Triad Scale here, and also learn about your light vs. dark triad balance.

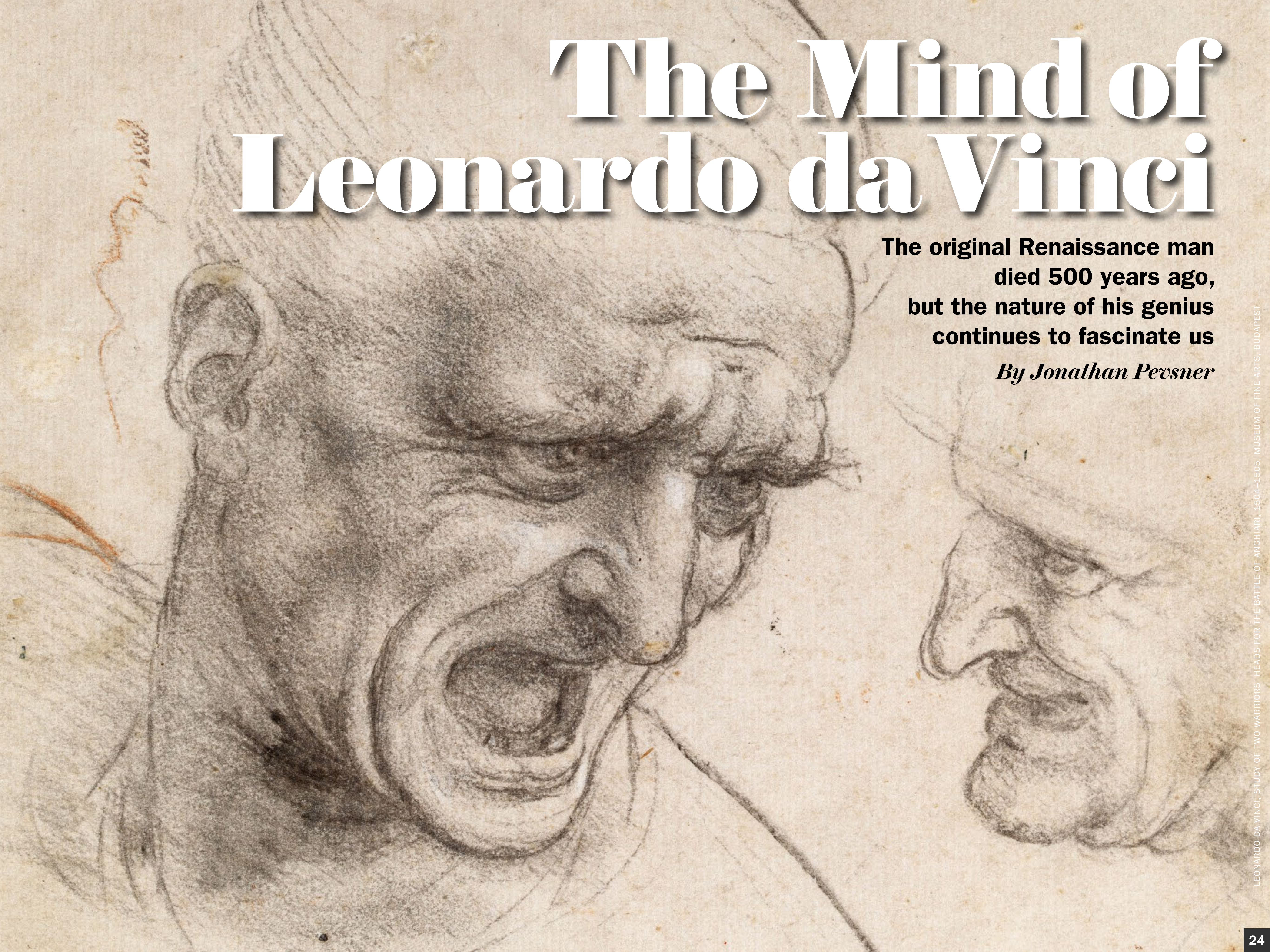
**This is in line with recent research on narcissism conducted by my colleagues and me that explicitly separates the antagonistic and agentic extraversion facets of narcissism in predicting well-being. We have found that the agentic extraversion aspect of narcissism is particularly adaptive when antagonism is partialed out of the equation.*

"THE LIGHT VS. DARK TRIAD OF PERSONALITY: CONTRASTING TWO VERY DIFFERENT PROFILES OF HUMAN NATURE," BY SCOTT BARRY KAUFMAN, DAVID YADEN, ELIZABETH HYDE AND ELI TSUKAYAMA, IN *FRONTIERS IN PSYCHOLOGY*; MARCH 12, 2019

The Mind of Leonardo da Vinci

The original Renaissance man died 500 years ago, but the nature of his genius continues to fascinate us

By Jonathan Pevsner



LEONARDO DA VINCI, STUDY OF TWO WARRIORS' HEADS FOR THE BATTLE OF ANGHIARI, 1504–1505. MUSEUM OF FINE ARTS, BUDAPEST

Jonathan Pevsner is a professor in the department of neurology at the Kennedy Krieger Institute and in the department of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine.

Across the centuries, each generation has interpreted Leonardo da Vinci (1452-1519), finding him to be remarkably modern. At the 500th anniversary of his death (May 2, 2019) we can consider Leonardo's meaning in our era. Our fundamental nature as human beings has not changed in 500 years, but our environment has transformed at an extraordinary rate, along with our perspectives on his accomplishments—and our own.

THE NATURE OF GENIUS

Leonardo is a genius and a potent symbol of the "universal man" because of the breadth of his interests in the arts, science and technology, spanning disciplines from chemistry (he discovered acetone) to astronomy (he discovered the lumen cinereum of the moon) to math (he discovered the center of gravity of a pyramid) to working with plastics.

Genius takes many forms, and in Leonardo's case we recognize his limitations. He was defensive about his lack of formal education; he called himself "*omo sanza lettere*" (a man without letters). He had trouble with basic arithmetic operations, and his Latin skills were weak. He surely would not have performed well in a modern school system, and his IQ might have been tested as low. (I do not believe he can or should be diagnosed with any condition such as autism spectrum disorder or attention-deficit/hyperactivity disorder.)

Many people wonder if there could be a genius like Leonardo today, or what a person of his disposition would do. Perhaps there cannot be another like him because today's world requires tremendous specialization. Many of us are in fields that demand interdisciplinary thinking. But few scientists, physicians, poets or politicians today are called geniuses.

A UNIFIED VISION OF NATURE'S LAWS

Leonardo's science was grounded in the Aristotelian world as shaped by 18 centuries of interpreters. He developed a system of what he called the four powers of nature: movement, weight, force and percussion. Although he struggled to define these concepts, and many of the ideas are archaic, it is telling that he developed a coherent model for all natural phenomena ranging from the macrocosm (e.g., geological forces that lead to the formation of rivers and oceans) to the microcosm (e.g., human anatomy).

I believe he was excited about his conception of the four powers and how they informed his art and science. We are on a similar kind of path today, seeking the grand unification of the laws of physics as we study natural phenomena from subatomic particles to the history of the universe. Few of us extend this attempt at unification to the arts as well.

VISUALIZED KNOWLEDGE

To Leonardo, vision is the noblest of the senses and of paramount importance, and his passion for vision was extreme. "The eye is the window of the human body through which the soul views and enjoys the beauties of the world. Because of it, the soul is content in its human prison, and without it this human prison is its torment" he writes in his *Paragone* (comparison of the arts). He emphasized ways to visualize knowledge and he pioneered anatomical illustration.

To Leonardo, painting was a science, and the creative act of painting is useful to visualize the world. As an anatomist and physiologist he decided at one point that the sense of vision is so important that it must be mediated by its own brain region, the "*imprensiva*."

Seeing also has the meaning of paying attention, and Leonardo did this with exquisite patience. He would strike a dusty table and describe the pattern by which the dust settled again. He performed repeated dissections of the body, and when his observations conflicted with those

of his authorities, he was sometimes able to liberate himself and pioneer original discoveries.

FAITH IN EXPERIENCE

Leonardo was most comfortable relying on his senses as the basis of meaningful experience. He summarizes his attitude about the surety of science. "To me it seems that those sciences are vain and full of error which are not born of experience, mother of all certainty, firsthand experience which in its origins, or means, or end has passed through one of the five senses. And if we doubt the certainty of everything which passes through the senses, how much more ought we to doubt things contrary to these senses such as the existence of god or of the soul or similar things over which there is always dispute and contention," he writes in his *Treatise on Painting*. For Leonardo, this faith in experience was largely visual. In the 21st century we understand we cannot derive all knowledge from sensory experience, and many us studying genomes or otherwise using computers have encountered the limits of empiricism. Confronted with today's world, no doubt Leonardo would have been brilliant at visualizing information.

INTERDISCIPLINARY SCIENCE

Leonardo's thinking was interdisciplinary. When he injected wax into the brain or into the heart to make casts of the inner workings of the body, he was borrowing the "lost wax" technique familiar to sculptors. When he studied friction and invented roller bearings and ball bearings, he reasoned that frictional resistance differs according to the nature of the surfaces in contact, and increases in direct proportion to load, and he even estimated (for the first time) a coefficient of friction. But he went further to realize its relevance not just to machines but to the movements of tendons over bones; to the creation of heat by the heart; and to the production of voice by the friction of air on the vocal cords.

CREATIVITY IN SCIENCE AND ART

Creativity is productivity marked by imagination. Creativity is as basic to art as to science. We can be creative as teachers, as students, as writers and readers. We can appreciate the many facets of Leonardo's creativity, and it can inspire us today.

Leonardo combined science, art and engineering in a unique way. In his time "*scientia*" referred to knowledge while "*ars*" referred to manual proficiency. The modern distinction between the sciences and humanities, famously described by C. P. Snow, did not exist as it does today. Leonardo was well positioned as an artist to assume the mission of a scientist. For Leonardo, the artist's creative, noble purpose is to depict the natural world. The artist must understand the entire world as a scientist would.

FULFILLMENT OF HUMAN POTENTIAL

Today we can appreciate all that Leonardo accomplished, as well as his many failures, seeing someone who fulfilled his potential in a unique way. He was appreciated as an extraordinary artist in his own lifetime, and his admirers had a sense that his explorations of the worlds of science and engineering were exceptional. He has inspired generations for 500 years, with our appreciation growing in the past century as we have been able to interpret his writings.

As ever-increasing access to information and technology shapes today's world, we as a society may reflect on Leonardo's values of creativity, curiosity, talent and knowing how to see. We admire his values, and we may wonder how they fit into contemporary society. I am not sure he would have thrived. We can also wonder how his values could help each of us try to fulfill our own potential; from this point of view, millions of us are inspired by his life's journey.

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OBSERVATIONS

How Language Shapes the Brain

The ascent of Japan's Emperor Naruhito offers a lesson in the neuroscientific power of words

When Emperor Akihito stepped down from the Chrysanthemum Throne on May 1, 2019, in Japan's first abdication in 200 years, Naruhito officially became the new emperor ushering in a new era called *Reiwa* (令和; "harmony"). Japan's tradition of naming eras reflects the ancient belief in the divine spirit of language. *Kotodama* (言霊; "word spirit") is the idea that words have an almost magical power to alter physical reality. Through its pervasive impact on society, including its influence on superstitions and social etiquette, traditional poetry and modern pop songs, the word *kotodama* has, in a way, provided proof of its own concept.

For centuries, many cultures have believed in the spiritual force of language. Over time, these ideas have extended from the realm of magic and mythology to become a topic of scientific investigation—ultimately leading to the discovery that language can indeed affect the physical world, for example, by altering our physiology.

Our bodies evolve to adapt to our environments, not only over millions of years but also over the days and years of an individual's life. For instance, off the coast of Thailand, there are children who can "see like dolphins." Cultural and environmental factors have shaped how these sea nomads of the Moken tribe conduct their daily lives, allowing them to adjust their pupils underwater in a way that most of us cannot.

Just as extensive diving can change our pupils,

LIZZIE ROBERTS *GETTY IMAGES*

and exercise can change our bodies, so can mental activity, such as learning and using language, shape the physical structures of our brains. When two neurons respond to a stimulus (such as a word), they begin to form chemical and physical pathways to each other, which are strengthened or weakened depending on how often they are co-activated. This process of "neurons that fire together, wire together" is the basis for all learning, and is reflected in the formation of gray matter (where neurons communicate with each other) and white matter (fatty tracts connecting gray matter regions).

The brain's ability to adapt to its environment explains how we become specialized to the sounds of our native tongue. All infants are born with the ability to discriminate between the speech sounds of different languages, but eventually become tuned to the inputs they hear the most; neural pathways corresponding to native phonemes are strengthened, while those corresponding to foreign sounds are pruned. For bilinguals, this window of "universal" sound processing stays open longer because of their exposure to richer language environments. In other words, the inputs that our brains receive shape how we experience the world around us.

Despite the fact that multilingualism is the norm rather than the exception, the monolingual model remains the standard for studying neurocognition. A review of over 180 studies recently published in the journal *Behavioral* and *Brain Functions* discusses how the challenges associated with juggling multiple languages can affect the way we perceive and respond to our surroundings, as well as the physical structure of the brain.

For example, neuroimaging has shown that bilingualism can enhance attention and sensitivity to sounds, even past infancy, and even if you begin to learn another language later in life. Bilingualism can also make your brain more efficient at managing the immense volume of information that comes streaming in on a second-to-second basis, helping you focus on what matters and ignore distracting inputs.

Both of these skills are critical for learning new languages, which may explain why learning a second language can make it easier for you to learn a third or a fourth. This is in stark contrast to older, now debunked, ideas that the brain only has room for one language (as if the brain divides up a fixed amount of space among languages, as opposed to being an active living organ with dense and interacting connections). Learning a new language changes, and even optimizes, how you use what you already have.

To illustrate, extensive exposure to multilingual speech can result in more robust encoding of sounds in the evolutionarily ancient brain stem, as well as increased gray and white matter in the primary auditory cortex. As a result, after training, even adults may find it easier to perceive foreign speech sounds, as well as mimic foreign accents, compared to monolinguals.

Decoding complex speech signals is just one challenge encountered by the bilingual brain. As a spoken word unfolds (e.g., "c-a-n-d-l-e"), both monolinguals and bilinguals need to suppress interference from similar words that come to mind (e.g., "cat," "can," "candy"). However, in addition to similar words from the same language, multilinguals also consider words from other languages they know.

In fact, the bilingual brain is always ready to process words from all known languages—multiplying the number of so-called linguistic competitors. Over time, bilinguals can become experts at controlling these competitors, to the point where the brain regions that monolinguals rely on to resolve within-language competition (e.g., the anterior cingulate cortex) show less activation for bilinguals unless they need to manage competition across languages.

Just as having stronger muscles allows you to lift weights with less effort, increased gray matter in classic executive control regions may make it easier for bilinguals to manage irrelevant information. Bilinguals also have increased white matter in the tracts connecting frontal control areas to posterior and subcortical sensory and motor regions, which may allow them to off-load some of the work to areas that handle more procedural activities. Because the same neural machinery can be used for both linguistic and nonlinguistic tasks, multilingual experience can even affect performance in contexts that involve no language at all.

Increased gray and white matter, as well as the ability to flexibly recruit different brain regions, may help explain why bilingualism can delay the onset of dementia symptoms by four to six years. Fortunately, there doesn't appear to be a deadline for fortifying your brain, as learning a foreign lan-

guage can still have an impact well into adulthood and after relatively brief amounts of training. Furthermore, changes to one area or function are likely to have cascading effects; better cognitive control can enhance auditory processing, which may facilitate further language learning and continued neural restructuring.

The human capacity for language has played a critical role in the development of civilizations, the transmission of knowledge and our ability to collectively shape our environments. Mythology and magic aside, endowing the new Japanese era with the word *Reiwa* could have tangible outcomes by influencing people's thoughts and choices.

While such external consequences of language have been observable throughout history, we have only recently acquired tools such as fMRI, EEG, PET, MEG, NIRS, CT and eye tracking that enable us to see how language reaches back to shape the brain itself. We now know that experience with multiple languages can produce extensive changes to our neural architecture that are observable across the lifespan and across domains: from infancy to old age, from sensory perception to higher cognitive processing. Using and learning language can change our very biology, thereby confirming the ancient intuition that words can, in fact, alter physical reality.

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OBSERVATIONS

The Concept of Neurodiversity Is Dividing the Autism Community

It remains controversial—but it doesn't have to be

A teenager in a French autism education institute.

GETTY IMAGES

At the annual meeting of the International Society for Autism Research (INSAR) in Montreal, in May, one topic widely debated was the concept of neurodiversity. It is dividing the autism community, but it doesn't have to.

The term "neurodiversity" gained popular currency in recent years but was first used by Judy Singer, an Australian social scientist, herself autistic, and first appeared in print in the *Atlantic* in 1998.

Neurodiversity is related to the more familiar concept of biodiversity, and both are respectful ways of thinking about our planet and our communities. The notion of neurodiversity is very compatible with the civil-rights plea for minorities to be accorded dignity and acceptance, and not to be pathologized. And while the neurodiversity movement acknowledges that parents or autistic people may choose to try different interventions for specific symptoms that may be causing suffering, it challenges the default assumption that autism itself is a disease or disorder that needs to be eradicated, prevented, treated or cured.

Many autistic people—especially those who have intact language and no learning difficulties such that they can self-advocate—have adopted the neurodiversity framework, coining the term "neurotypical" to describe the majority brain and seeing autism as an example of diversity in the set of all possible diverse brains, none of which is "normal" and all of which are simply different.

They argue that in highly social and unpredictable environments some of their differences may manifest as disabilities, while in more autism-friendly environments the disabilities can be

minimized, allowing other differences to blossom as talents. The neurodiversity perspective reminds us that disability and even disorder may be about the person-environment fit. To quote an autistic person: "We are freshwater fish in salt water. Put us in fresh water and we function just fine. Put us in salt water and we struggle to survive."

There are also those who, while embracing some aspects of the concept of neurodiversity as applied to autism, argue that the severe challenges faced by many autistic people fit better within a more classical medical model. Many of these are parents of autistic children or autistic individuals who struggle substantially in any environment, who may have almost no language, exhibit severe learning difficulties, suffer gastrointestinal pain or epilepsy, appear to be in anguish for no apparent reason or lash out against themselves or others.

Many of those who adopt the medical model of autism call for prevention and cure of the serious impairments that can be associated with autism. In contrast, those who support neurodiversity see such language as a threat to autistic people's existence, no different than eugenics.

No wonder this concept is causing such divisions. Yet I argue that these viewpoints are not mutually exclusive and that we can integrate both by acknowledging that autism contains huge heterogeneity.

Before we address heterogeneity, a technical aside about terminology: The term "disorder" is used when an individual shows symptoms that are causing dysfunction and where the cause is unknown, while the term "disease" is used when a disorder can be ascribed to a specific causal mechanism. The term "disability" is used when an individual is below average on a standardized measure of functioning and when this causes suffering in a particular environment. In contrast, the term "difference" simply refers to variation in a trait, like having blue or brown eyes.

So what is the huge heterogeneity in the autism spectrum? One source of this is in language and intelligence: As I hinted at, some autistic people have no functional language and severe developmental delay (both of which I would view as disorders), others have milder learning difficulties, while yet others have average or excellent language skills and average or even high IQ.

What all individuals on the autism spectrum share in common are social communication difficulties (both are disabilities), difficulties adjusting to unexpected change (another disability), a love of repetition or "need for sameness," unusually narrow interests, and sensory hyper- and hypo-sensitivities (all examples of difference). Autism can also be associated with cognitive strengths and even talents, notably in attention to and memory for detail, and a strong drive to detect patterns (all of these are differences). How these are manifested is likely to be strongly influenced by language and IQ.

The other source of the huge heterogeneity is that autism is frequently accompanied by co-occurring conditions. I mentioned gastrointestinal pain or epilepsy (both examples of disorders and sometimes diseases), dyspraxia, ADHD and dyslexia (all examples of disabilities), and anxiety and depression (both examples of mental health conditions). This is just a partial list. A recent study shows that 50 percent of autistic people have at least four such co-occurring conditions (including language disorder or learning difficulties), and more than 95 percent of autistic children have at least one condition in addition to autism.

The relevance of this for the neurodiversity debate is that if we dip into the wide range of features that are seen in autism, we will find differences and disabilities (both compatible with the neurodiversity framework), and we will find examples of disorders and even diseases, which are more compatible with a medical than a neurodiversity model.

Regarding scientific evidence, there is evidence for both neurodiversity and disorder. For example, at the genetic level, about 5 to 15 percent of the variance in autism can be attributed to rare genetic variants/mutations, many of which cause not just autism but also severe developmental delays (disorder), while about 10 to 50 percent of the variance in autism can be attributed to common genetic variants such as single nucleotide polymorphisms (SNPs), which simply reflect individual differences or natural variation.

At the neural level, some regions of the autistic brain (such as the amygdala, in childhood) are larger, and others (such as the posterior section of the corpus callosum) are smaller. These are evidence of difference but not necessarily disorder. Early brain overgrowth is another sign of difference but not necessarily disorder.

Postmortem studies of the autistic brain reveal a greater number of neurons in the frontal lobe, sug-

gesting that there may be reduced apoptosis (or pruning of of neural connections) in autism, but again this may just be evidence for difference rather than disorder. Against this, structural differences in the language areas of the brain in autistic individuals who are minimally verbal are likely to be a sign of disorder.

Functional MRI (fMRI) studies at times show less or more brain activity during different tasks, and again this can be interpreted in terms of difference and disability, but not clearly evidence of disorder. On the other hand, where autistic individuals have demonstrable epilepsy with a clear electrophysiological signature, this is a sign of disorder or even disease.

At the behavioral and cognitive levels autistic people show both differences, signs of disability and disorder. For example, young autistic toddlers may look longer at nonsocial stimuli than at social stimuli, and autistic people may show their best performance on IQ tests on the Block Design subtest, perhaps reflecting their strong aptitude for attention to detail and disassembling complex information into its component parts.

Both of these are simply differences, compatible with the neurodiversity model. Aspects of social cognition reflect areas of disability in autism, and are often the reason they seek and receive a diagnosis. But if an autistic person has severe learning difficulties or is minimally verbal (defined as having fewer than 30 words), this is arguably beyond neurodiversity and more compatible with the medical model.

In sum, there is a case for all of the terms "disorder," "disability," "difference" and "disease" being applicable to different forms of autism or to the co-occurring conditions. Neurodiversity is a fact of nature; our brains are all different. So there is no point in being a neurodiversity denier, any more than being a biodiversity denier. But by taking a fine-grained look at the heterogeneity within autism we can see how sometimes the neurodiversity model fits autism very well, and that sometimes the disorder/medical model is a better explanation.

What is attractive about the neurodiversity model is that it doesn't pathologize and focus disproportionately on what the person struggles with, and instead takes a more balanced view, to give equal attention to what the person can do. In addition it recognizes that genetic or other kinds of biological variation are intrinsic to people's identity, their sense of self and personhood, which should be given equal respect alongside any other form of diversity, such as gender. But to encompass the breadth of the autism spectrum, we need to make space for the medical model too.

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.

OBSERVATIONS

Psychiatry's Inevitable Hubris

Can clinicians help their patients even in the absence of certainty?

GETTY IMAGES

It's 3 P.M. on a Saturday in March, and I'm working at Silver Hill Hospital. As the on-duty doctor, my job is to admit new patients and to work with the other staff to make sure that everything goes smoothly.

I'm about to see a young patient I'll call Adrian.* I glance in the glass-paned waiting room and notice Adrian sitting on the sofa. Their parents are also in the room (I'm using gender-neutral names and pronouns for the patients in this essay, as the author's note at the bottom explains), standing with concerned looks on their faces.

A few minutes later, I meet with Adrian, who turns out to be a pleasant college student. They've been feeling anxious and depressed and, in addition to worsening paranoid thoughts, is thinking about suicide.

Each patient is uniquely complex. I have never seen two identical patients: even within the same family, even among twins, patients are unique. Each patient's history and symptoms, brain and genes, hopes and fears differ, which is one reason why psychiatry is so difficult.

I need to figure out how to help Adrian. To do this, I need to reduce their complexity into something cognitively manageable, into something I can understand. The way I (and all clinicians) do this is to look for patterns: common symptoms and trends that help me understand what's going on and suggest a type of treatment.

A previous clinician had diagnosed Adrian with bipolar disorder, which means that the clinician had seen a particular pattern of symptoms and, accordingly, had begun them on a specific medication regimen. I sense a similar pattern as we discuss periods of mania and depression and, more recently, suicidality. We finish our conversation and return to the waiting room.

Adrian's parents are now sitting on the couch. The mother smiles, while the father looks deep in thought, staring out the window.

I ask them if they have any questions and Adri-

an's father replies quickly, "Well, I read this essay in the *Atlantic*—do you read the *Atlantic*?"

"Well, sometimes," I said, wondering if I looked too nerdy to be an *Atlantic* reader.

"The essay is called something like 'The Hubris of Psychiatry.' This guy is saying that psychiatrists don't know what's going on in the brain and so have made up names for all the disorders. If psychiatrists don't know what's going on, why should we bring our child to the hospital? Why should Adrian take medications with side effects if no one knows how they work?"

"PSYCHIATRY'S INCURABLE HUBRIS"

This article by Gary Greenberg, a practicing psychotherapist and successful writer, was in the *Atlantic*'s April 2019 issue. It's meant as a review of Anne Harrington's book *Mind Fixers*: *Psychiatry's Troubled Search for the Biology of Mental Illness*, but Greenberg uses it to discuss many of psychiatry's problems. He's a provocateur, and I like him for it.

Greenberg describes Harrington's book as "a tale of promising roads that turned out to be dead ends, of treatments that seemed miraculous in their day but barbaric in retrospect, of public-health policies that were born in hope but destined for disaster." Insulin comas, ice pick lobotomies, and ice baths (now-debunked treatments) are Greenberg's bogey men: look at how misguided psychiatrists have been!

Greenberg has told this story before. His own books, *Manufacturing Depression: The Secret History of a Modern Disease* and, more recently, *The Book of Woe: The* DSM *and the Unmaking of Psychiatry,* send more of the same into the ether. His many essays for the *New Yorker* and *Harper's* tell similar stories.

Greenberg wants psychiatrists (and everyone?) to admit that nothing is certain. Here's how he puts it:

"Even as psychiatrists prescribe a widening variety of treatments, none of them can say exactly why any of these biological therapies work. It follows that psychiatrists also cannot precisely predict for whom and under what conditions their treatments will work."

Greenberg demonstrates—so elegantly!—that the root problem is that psychiatrists and neuroscientists and pharmacologists and psychotherapists (himself included, presumably?) lack an exhaustive understanding of the brain. Greenberg is (understandably) uncomfortable that, well, dammit, we aren't wizards. Without such omniscience, he concludes, it is.

"Little wonder that the history of such a field—reliant on the authority of scientific m edicine even in the absence of scientific findings—is a record not only of promise and setback, but of hubris."

Well, I'm uncomfortable with uncertainty too. It sucks. I share Greenberg's contempt for sloppy, authority-based thinking. I've written about the imprecise nature of diagnosis and my quibbles with the DSM. As a clinical researcher who studies the brain, I confront and reckon with this uncertainty every day. But I've still got patients to treat.

TO TREAT OR NOT TO TREAT

"All of these medicines, but none of them are helping." Adrian's father continues, "Why even bother? It looks like we're just doing a lot of guessing without any precision. And there are serious side effects."

"Look, I'm the first to admit that our diagnoses are imprecise." I explain that I'd recently published an essay outlining exactly why I feel my diagnoses are imprecise.

"I guess it boils down to what the goal of the diagnostic process is," I say. "And also what you're willing to do once you think you understand the problem."

I tell him how, as a medical student, I'd come across the Ebers Papyrus, an ancient Egyptian medical text that explains patterns of symptoms, what they mean and how to treat that symptom pattern. If you see an arm that bends where it's not supposed to, you diagnose a broken arm, and you should set the arm, and so on.

What I liked about ancient Egyptian medicine wasn't just what they would do, but what they wouldn't do. For example, if you see a bump that keeps growing and growing, it's a "tumor against the god Xenus." This, the papyrus states, "thou shalt not treat…. Do thou nothing there against." They realized they didn't have an effective treatment and, in the absence of a definitive solution (based on their best understanding, that is; many treatments were literally snake oil), they simply wouldn't do anything. Better to not act than act with hubris.

"I really like that honesty," I confess. "But I suppose the problem is that doing nothing changes nothing, which in some cases isn't a good option."

"So here we are at Silver Hill Hospital." I motion

with my hands around the room. "You brought Adrian here because you're concerned your child may try to kill themself. Based on my conversation with them, I agree it's a serious risk and you're right to be concerned. People commit suicide every hour of every day. Now, let's say there's an 85 percent risk that Adrian might kill themself." The father nods.

"Now suppose that I told you there was a medicine that I thought might help. I wasn't sure that it'd work, but multiple, large studies have shown it might have, say, from a 20 percent to a 40 percent chance of working. Would you take it?"

"Of course," Adrian's father says with a smile. He knew where I was going.

"So right now, we're admitting Adrian to the hospital because, like anyone, being here decreases the likelihood that they'll kill themself. And we're also trying medications and therapies that very well might not work. They've worked in many people, but our science isn't advanced enough to predict whether they'll work for Adrian. But we're okay with that because Adrian's safe in the hospital and so, if one medication doesn't work, we can try another. We can keep trying things as long as Adrian's alive, but if they're dead, we're done. We can't help someone who's dead."

THE HUBRIS OF DOCTORING

A few weeks later, I'm back at Silver Hill Hospital. I'm making my rounds and I see Adrian at one of the transitional living facilities, which serves as a midway point between an inpatient unit and returning home. I stop to chat, to ask how they're doing.

"Good. I'm applying to get back in school now," Adrian says, pointing to an application on their lap. "Things are going better."

I mention that a few of my friends sent me Greenberg's essay and asked me the same questions we discussed a couple weeks ago. I ask Adrian if I can write about our conversation, whether I can tell their story, changing their name to protect their privacy. They nod and smile, "Of course." Later, I call their parents and ask them the same. Adrian's mother is on board and before my first admission for the day arrives, I begin this essay.

My first admission is another young patient with bipolar disorder. Similar to—but not precisely like—Adrian, this patient wants to die.

We sit down in the same exam room, "My name's Dr. Barron, I'm the admitting doctor today. Can you help me understand what's going on?"

"Since my first manic episode two years ago, my condition has been unbearable. I feel like I'm not living life, I'm just surviving. I'm tired of waiting four to six weeks just to see if a medication works. They don't. Nothing is yielding results. I'm unable to drive, read, work, draw—even silly pictures and I'm an artist—I can't even watch TV. Not even TV," they pause for the first time. I wonder if they're out of breath or thinking or both.

"I have severe anhedonia that's not being fixed by DBT, IPT or CBT. I think every minute about committing suicide because I can't handle this anymore. I can't handle this anymore," they say, hands covering their face as they lean forward in their chair. I notice the haggard black polish at the end of half an inch of nail bed. They're on the verge of tears.

They take a deep breath, "Every day I do nothing. I sit in my house and do nothing. Can you imagine what that feels like?"

They begin to cry. My stomach stirs and a tingle passes from my shoulders to my neck to the top of my head. My eyes begin to water as I shake my head, "No. I can't imagine what that feels like. I'm sorry."

I'm struck with irony. I realize I can't promise anything with certainty. I tell them this. We sit for a moment in silence.

Then I repeat—nearly verbatim—the conversation I had with Adrian and their parents. "I'm not sure that anything will work, but are you willing to try?" I ask.

Later, as I write my admission note, I wonder what I'm doing, whether it's hubris to do anything in the absence of certainty.

Does this patient have bipolar disorder? At this moment, I don't know. Will the medications I'm prescribing help? I don't know. Will anything I do help? I don't know.

I don't know, but it's my job to try. Maybe it's hubris, but then, maybe I can tip the scales in their favor.

**Author's Note: To protect the privacy of those involved, I agreed to not used their real names. I have further omitted (but not changed) details that are too sensitive or identifying. To this end, I have chosen to use gender-neutral pronouns to disguise both patients' genders. All of the events are true. The conversations I re-create come from my clinical notes and my clear recollections of them, though they are not written to represent word-for-word transcripts. The views expressed above are my own and not necessarily those of Silver Hill Hospital.*

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