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Do You Really Know Yourself?

10 surprising reasons
the answer is probably no

PLUS

- Useful Insecurities
- The Autism-Labeling Debate
- A New Treatment for Depression



FROM THE EDITOR

The Introspection Illusion

On a recent trip, I stopped in at the Art Institute of Chicago, which has a marvelous collection of Impressionist paintings. Among them, a self-portrait of Vincent van Gogh, completed in 1887 and one of the dozens of self-portraits the artist would complete in his lifetime. To me, this particular version is one of the broodier iterations, with the subject's striking blue-green eyes seeming to emanate a kind of melancholy. I couldn't help but wonder if van Gogh's many self-portraits were an endeavor to know himself better—or perhaps know the version that friends and passersby might describe.

To be sure, we humans are fascinated by ourselves, and yet research shows that our self-image is quite different from reality. As Steve Ayan writes in “[10 Things You Don't Know about Yourself](#),” our knowledge of ourselves can be distorted, and yet it can influence how we behave. But perhaps being a mystery to ourselves isn't such a bad thing. As Ellen Hendrickson writes in “[Why Everyone Is Insecure \(and Why That's Okay\)](#),” “a healthy dose of self-doubt spurs us to monitor ourselves and our interactions. It prompts introspection and helps us identify how to get along better with our fellow humans.”

Elsewhere in this issue, Alison Abbott covers a promising new area of research on the impact that immune molecules in the brain have on dementia and neurodegenerative disorders. Read more in “[Is 'Friendly Fire' in the Brain Provoking Alzheimer's Disease?](#)” As always, we love your feedback!

Andrea Gawrylewski

Collections Editor: editors@sciam.com



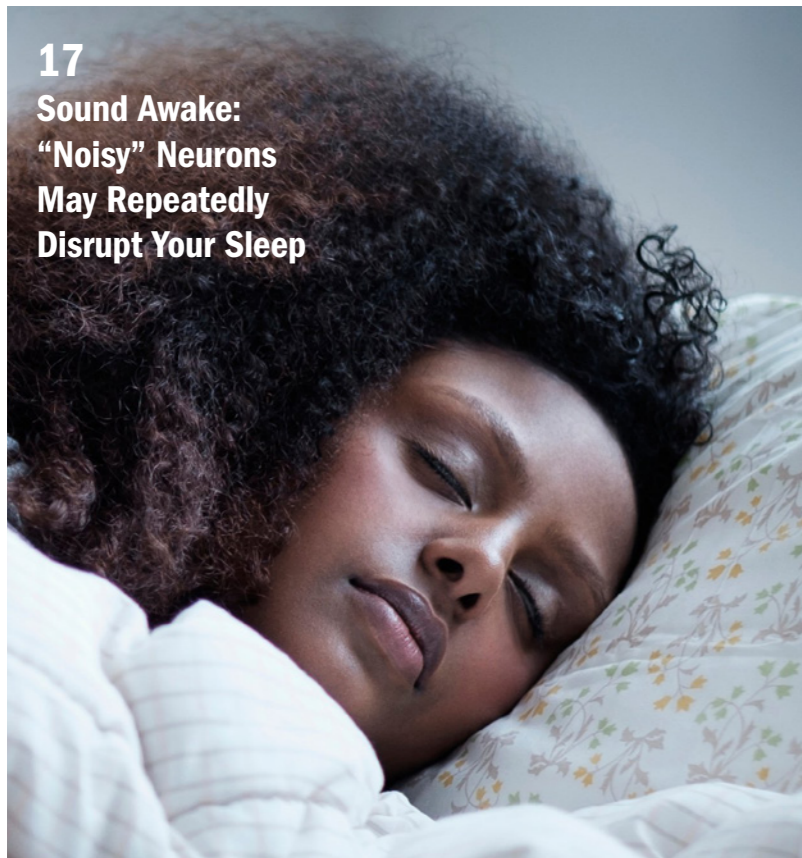
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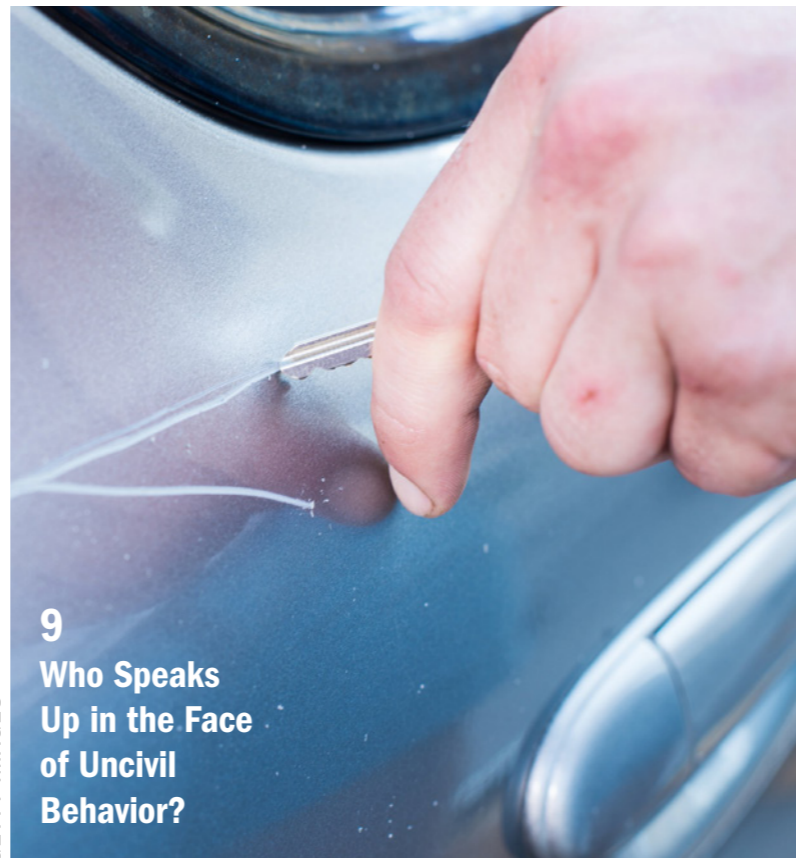
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NEWS

At What Age Does Our Ability to Learn a New Language Like a Native Speaker Disappear?

Despite the conventional wisdom, a new study shows picking up the subtleties of grammar in a second language does not fade until well into the teens

The older you get the more difficult it is to learn to speak French like a Parisian. But no one knows exactly what the cutoff point is—at what age it becomes harder, for instance, to pick up noun-verb agreements in a new language. In one of the largest linguistics studies ever conducted—a viral internet survey that drew two thirds of a million respondents—researchers from three Boston-based universities showed children are proficient at learning a second language up until the age of 18, roughly 10 years later than earlier estimates. But the study also showed that it is best to start by age 10 if you want to achieve the grammatical fluency of a native speaker.

To parse this problem, the research team, which included psychologist Steven Pinker of Harvard University, collected data on a person's current age, language proficiency and time studying English. The investigators calculated they needed more than half a million people to make a fair estimate of when the “critical period” for achieving the highest levels of grammatical fluency ends. So they turned to the world's greatest experimental subject pool: the internet.

They created a short online grammar

quiz called Which English? that tested noun-verb agreement, pronouns, prepositions and relative clauses, among other linguistic elements. From the responses, an algorithm predicted the tester's native language and which dialect of English (that is, Canadian, Irish, Australian) they spoke. For example, some of the questions included phrases a Chicagoan would deem grammatically incorrect but a Manitoban would think is perfectly acceptable English.

The researchers got a huge response by providing respondents with “something that is intrinsically rewarding,” says Joshua Hartshorne, an assistant professor of psychology at Boston College, who led the study while he was a postdoc at the Massachusetts Institute of Technology. The small gift to the respondents was a guess about their background. According to Hartshorne: “If it correctly figures out that you are in fact a German-American, people are like, ‘Oh my god, science is awesome!’ And when it's wrong, they're like, ‘Ha ha, stupid robot.’ Either way, it's entertaining and interesting and something that they can think about and talk about with their friends.”

Hartshorne's tactic worked. At its peak, the quiz attracted 100,000 hits a day. It was

shared 300,000 times on Facebook, made the front page of Reddit and became a trending topic on 4chan, where a thoughtful discussion ensued about how the algorithm could determine dialect from the grammar questions. The study brought in native speakers of 38 different languages, including 1 percent of Finland's population.

Based on people's grammar scores and information about their learning of English, the researchers developed models that predicted how long it takes to become fluent in a language and the best age to start learning. They concluded that the ability to learn a new language, at least grammatically, is strongest until the age of 18 after which there is a precipitous decline. To become completely fluent, however, learning should start before the age of 10.

There are three main ideas as to why language-learning ability declines at 18: social changes, interference from one's primary language and continuing brain development. At 18, kids typically graduate high school and go on to start college or enter the work force full-time. Once they do, they may no longer have the time, opportunity or learning environment to study a second language like they did when they were

younger. Alternatively, it is possible that after one masters a first language, its rules interfere with the ability to learn a second. Finally, changes in the brain that continue during the late teens and early 20s may somehow make learning harder.

This is not to say that we cannot learn a new language if we are over 20. There are numerous examples of people who pick up a language later in life, and our ability to learn new vocabulary appears to remain constant, but most of us will not be able to master grammar like a native speaker—or probably sound like one either. Being a written quiz, the study could not test for accent, but prior research places the critical period for speech sounds even earlier.

Although the study was conducted only in English, the researchers believe the findings will transfer to other languages, and they are currently developing similar tests for Spanish and Mandarin.

Perhaps even more important than when one learns a language is how. People who learned via immersion—living in an English-speaking country more than 90 percent of the time—were significantly more fluent than those who learned in a class. Hartshorne says that if you have the choice

Perhaps even more important than when one learns a language is how.

between starting language lessons earlier or learning through immersion later, “I’d learn in an immersion environment. Immersion has an enormous effect in our data—large even relative to fairly large differences in age.”

In what could be the most surprising conclusion, the researchers say that even among native speakers it takes 30 years to fully master a language. The study showed a slight improvement—roughly one percentage point—in people who have been speaking English for 30 versus 20 years. The finding is consistent for both native and non-native speakers.

Charles Yang, a computational linguist at the University of Pennsylvania, says this finding does not surprise him, given the sophisticated grammar rules that we do not pick up until our teenage years—how to change an adjective into a noun, for instance. “These are going to be very fine-

grained details in the language,” he says. “You’re learning new words and you’re learning some morphological endings when you’re quite old, you know, in the teenage years.”

The enthusiasm for the study is not shared by everyone in the field. Elissa Newport, a professor of neurology at Georgetown University who specializes in language acquisition, remains a skeptic. “Most of the literature finds that learning the syntax and morphology of a language is done in about five years, not 30,” she says. “The claim that it takes 30 years to learn a language just doesn’t fit with any other findings.”

Newport says that although the premise of the study—seeking critical periods for learning a language—is warranted, she thinks the surprising results emerged because the measure the researchers used is flawed. “Testing 600,000 people doesn’t give you a dependable, reliable outcome” if

you're not asking the right questions, she says. Instead of creating a new test, Newport says she would have preferred the researchers use an existing assessment of language proficiency to ensure they are really gauging how well people know English.

Hartshorne is hoping to re-create the success of Which English? in a new online vocabulary test, but says he has struggled to create the same level of viral response because people are less willing to share their results if they perform poorly. "When you find out, 'I'm in the 99th percentile of vocabulary,' you're like, 'Okay, click, share.' But you know 50 percent of people are below average. And they're going to be less likely to want to share that."

— DANA G. SMITH



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NEWS

Who Speaks Up in the Face of Uncivil Behavior?

Psychologists develop a theory of who stands up, and who lets it pass

Have you ever been out in public and seen someone do something outrageous? Maybe you witnessed someone yelling a racial slur at a stranger or physically abusing a young child in their care. All of us probably remember a time when someone's behavior violated our standards of moral decency, but only some of us can say we actively intervened. What separates those who speak up from those who stay silent?

On the one hand, you might hypothesize that people who are more aggressive or hostile by nature are more likely to openly challenge a stranger. On the other hand, speaking out against injustice could be seen in a more positive light, as an act of maturity. Emerging research supports the latter idea—that people who stand up to incivility have a strong sense of altruism, combined with self-confidence. Understanding what motivates these heroic individuals could lead to more effective ways of curbing everyday immoral behavior.

Psychologist Alexandrina Moisuc of the University of Clermont Auvergne in France and her colleagues recently published findings from three studies looking at the personality profile possessed by people who

Perhaps future studies will look at the relationship between personality traits and people's willingness to intervene in a staged scenario.

say they would intervene in the face of bad behavior. Although there has been extensive research on how situational factors can impact people's motivation to intervene (the bystander effect), there have been fewer studies looking at the role of personality.

The researchers tested two competing and equally plausible theories about who stands up: the “bitter complainer” versus the “well-adjusted leader.” The “bitter complainer” theory suggests that hostile, aggressive and insecure people are more likely to become vigilantes out of a desire to unleash displaced frustration onto an unsuspecting target. In contrast, the “well-adjusted leader” theory takes the view that people who intervene are more likely to be confident, stable and mature.

In an initial study, the researchers recruited 291 Austrian students to watch six

short video clips online showing a person engaging in various types of uncivil behavior. For example, in one video the person was shown kicking a can of beer several times and then leaving it on the ground without picking it up. In another video a person is shown sitting on a bench and making an obscene gesture to a woman walking by. In all instances, the person in the video was depicted as a young man wearing regular, average clothes. After watching each video, participants rated the emotions they were feeling such as fear, disdain and disgust. These emotion ratings were combined to provide an overall measure of “moral outrage” for each participant. Next the participants were asked how they would have reacted if they had encountered the behavior in the video in their real lives. They rated the likelihood they

would have done each of the following: had no reaction at all, given the person a disapproving look, made a loud and audible sigh, alerted an authority such as the police, made a disapproving comment not directly addressed to the person, made a polite comment to the person, or made an aggressive comment to the person. Participants also filled out a number of other questionnaires that measured various dimensions of their personalities such as altruism and self-esteem.

Overall, the findings seemed to support the “well-adjusted leader” theory rather than the “bitter complainer” hypothesis. People who said they would react to the behaviors depicted in the videos felt more moral outrage (stronger feelings of anger and disgust), but they did not appear to be inherently more aggressive than other people, as measured by a personality scale. Instead, they scored higher on a measure of altruism, suggesting that their motivation to act was coming from a place of wanting to help others rather than harm the person engaging in the bad behavior.

However, before drawing firm conclusions, the researchers sought to replicate and extend their findings in two additional

Moisuc and her colleagues seem to have found that people who stand up in the face of uncivil behaviors are the opposite of complainers.

studies that included a more diverse sample of working adults. Participants in these studies read about a greater variety of scenarios where people engaged in uncivil or immoral acts. For example, they read about a person who left dog droppings on the sidewalk without picking them up and another where a man at a public zoo hits his three-year-old son in the face. Again, participants rated the likelihood that they would say or do something in reaction to the immoral behavior. They also filled out a number of questionnaires measuring their various personality traits. Once again, the findings showed support for the “well-adjusted leader” hypothesis: participants who reported that they would have reacted in some way to the outrageous behavior showed a number of positive personality traits including self-acceptance,

social responsibility and independence. They also tended to report having better control over their emotions. Also, aggression was again unrelated to the tendency to speak up, as was empathy, self-esteem, gender and occupation. Being older and having a higher salary did correlate with intervening, suggesting that feeling more secure or confident in one’s social position in society might be related to a willingness to react.

If anything, Moisuc and her colleagues seem to have found that people who stand up in the face of uncivil behaviors are the opposite of complainers. Instead they seem to possess traits that characterize upstanding citizens: a strong desire to help others, self-confidence, security in one’s place in society and maturity in handling their own emotions. Other research has supported

the idea that people who intervene have a more positive outlook on others. Psychologists Aneeta Rattan of London Business School and Carol Dweck of Stanford University found that people who believe that others have the capacity to change are more likely to confront prejudice.

A major limitation of this research is that it is based on people's self-reports rather than a measure of actual behavior. Perhaps future studies will look at the relationship between personality traits and people's willingness to intervene in a staged scenario. However, the results remain important for helping us understand how to promote a more civil society. After all, the willingness to openly express disapproval in the face of immorality, or even step in and try to directly intervene, is often the first and most direct path toward social change.

— DAISY GREWAL

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NEWS

Can a Pill That Boosts “Resilience” Treat Depression?

A clinical trial tests a new way to
reverse the psychiatric disorder

Self-help books often extoll the value of resilience. Last year one such primer—*Bounce: Overcoming Adversity, Building Resilience and Finding Joy*—proclaimed: “By strengthening your inner power, your ability to handle stressful situations and your skill in persevering after setbacks threaten to fell you, you’ll develop real resilience—you’ll develop grit.”

This implies weathering adverse life events is a character trait to be cultivated. Exercising, eating right and giving yourself mental pep talks certainly may help. But neuroscientists are learning the story is not quite so simple, and that some people are likely better equipped from birth to deal with adversity. During the last 15 years discoveries about why some brains excel at resisting stress have initiated a search for new drugs to treat depression and post-traumatic stress disorder by enhancing psychological resilience. One of these compounds has now entered early-stage clinical trials.

If the drug is safe and works, it will undoubtedly encounter strong demand; depression—the world’s leading cause of mental disability—never enters full remission in more than half the patients treated

with psychotherapies and existing antidepressants.

But depression does not affect everyone, and the molecular biology of resilience for psychiatric disorders can be clearly seen by inspecting the brains of lab animals. About a third of mice exposed to severe stress (in the form of aggressive attacks by other rodents) seem to breeze through these assaults without developing the social withdrawal, listlessness or other depression and traumalike symptoms displayed by most of their rodent lab-mates.

Observing this seemingly adaptive behavior, investigators started to probe the genetics and neurochemistry that distinguish the more resistant animals. In stressed mice there is a dramatic rise in the activity of certain genes in the nervous system—as if these rodents’ brains had set in motion a set of protective measures to cope with the trauma. “Manyfold more genes were regulated in the resilient animals than in the susceptible animals across several brain regions,” says Eric Nestler, director of the Friedman Brain Institute at the Icahn School of Medicine at Mount Sinai. “That was a real surprise to us.” (Nestler was at The University of Texas Southwestern Medical Center

when his group started studying what researchers call chronic social defeat stress.)

New York City’s Mount Sinai Hospital has become a nexus for resilience research, with studies conducted by several laboratories on both the psychology and neurobiology of adapting to stress. In 2014 pharmacologist and neuroscientist Ming-Hu Han and a group of his Mount Sinai colleagues published a paper in *Science* showing how out-of-whack electrical signaling in neurons populating the brain’s reward system could explain why some lab animals were susceptible to depression whereas others remained resilient.

Looking inside the brains of animals exposed to chronic social defeat stress, the scientists observed hyperactive firing of neurons in the ventral tegmental area (VTA), a critical part of a reward circuit. When things go awry, this manic firing of cells in the VTA contributes to the lack of motivation experienced in depression.

The resilient mice, however, held a surprise for Han and his team. The VTAs in their brains exhibited even greater levels of frenzied electrical activity than those of their more vulnerable counterparts—but only for a brief period. In the naturally re-

silient animals the higher neural activity seemed to induce a counterreaction that resulted in the subsequent quieting of overactive neurons. “This is one of the most important unexpected findings in the 2014 *Science* paper,” Han says. “Too big a pathophysiological alteration triggers a compensatory rebound.”

The Han team took things one step further to see if they could help the nonresilient animals through artificial means. When the researchers gave the mice a drug called lamotrigine, often prescribed for bipolar disorder, the animals’ brain activity mimicked that of their resilient counterparts: The neurons in the already hyperactive VTA started firing even more intensely, followed by a lull and abatement of depression symptoms.

Around this time the various resilience research groups at Mount Sinai convened for a monthly gathering referred to informally as “The Depression Club.” Han told the group about a set of compounds—all existing drugs—that help open channels in the outer membrane of cells in the VTA. When dosed with the drugs, these neurons, which produce the signaling molecule dopamine, let positively charged ions leave the cell,

“It was successful in the sense that we did see antidepressant effects, with the important caveat that there was no placebo group.”

thereby damping the cells’ hyperactive firing. This in turn tamps down depression symptoms. Based on Han’s presentation to the Depression Club, the group decided to move forward with a clinical trial in patients. The study—led by James Murrough, assistant professor of psychiatry and director of the Mood and Anxiety Disorders Program at Mount Sinai—chose the epilepsy drug ezogabine, which was given to 18 patients in a pilot trial.

Brain scans showed the drug affected the same reward circuit that it did in animals. “It was successful in the sense that we did see antidepressant effects, with the important caveat that there was no placebo group,” Murrough says. A larger placebo-controlled clinical trial, sponsored by the National Institute of Mental Health (NIMH), is now underway. (GlaxoSmith-

Kline has decided to stop marketing ezogabine but other existing drugs that also operate by tweaking potassium channels in brain cells—or a wholly new class of compounds—could serve in its place.)

The idea of a resilience pill seems compelling to some researchers not directly involved with the Mount Sinai research. “The ability to provide a treatment that can increase stress resiliency at the cellular level, and hopefully also the behavioral level, would be a much welcomed addition to our antidepressant armamentarium,” says Gerard Sanacora, a professor of psychiatry at Yale University School of Medicine and director of the Yale Depression Research Program. He cautions, however, about drawing too many conclusions from animal studies and early-stage clinical trials. He cites his own group’s experience with a novel anti-

depressant candidate that initially looked promising but failed in a placebo-controlled trial.

Moving forward with a potential resilience pill is warranted, however, notes Robert Sapolsky, a Stanford University professor of neuroscience. “There’s such a massive number of people with serious depression who aren’t helped by current drugs that it’s most definitely worth a try.” The approach pursued by Mount Sinai investigators “has been really novel,” Sapolsky says, “focusing on very reductive mechanisms explaining why VTA neurons become hyperactive in mice destined for stress-induced depression, and not in resistant animals.”

One caveat comes from David Nutt of Imperial College London. He points out that like new resilience drug candidates, standard depression treatments like Prozac diminish hyperactivity in neurons—but in a different set of cells. “I think that resilience is how the current antidepressant drugs work,” Nutt says. The neuropsychopharmacologist suggests a more novel approach might involve psychedelic drugs such as psilocybin, which have potential antidepressant effects.

Ezogabine represents only one means to

potentially enhance resilience. Researchers at Mount Sinai and elsewhere are considering other ways of regulating the reward system as well as modulating gene activity and the brain’s signaling molecules, or neurotransmitters.

Unlike many clinical trials that emphasize relief of symptoms as their primary objective, the ezogabine study’s goal is to gauge how well the therapy addresses some of the biological underpinnings of depression—in this case, whether the drug lessens the hyperactivity of the reward circuit that includes VTA neurons. The NIMH has focused recently on targeting disease mechanisms in research it funds, because symptoms overlap for many psychiatric disorders. Whether this approach works better in developing drugs for psychiatric disorders remains to be proved. But it is worth exploring; conventional clinical trials have repeatedly come up empty.

— GARY STIX

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NEWS

Sound Awake: “Noisy” Neurons May Repeatedly Disrupt Your Sleep

Study proposes novel sleep theory, but whether it can explain infant death syndrome remains less clear

You don't remember it, but you woke up at least 100 times last night. These spontaneous arousals, lasting less than 15 seconds each, occur roughly every five minutes and don't seem to affect how well-rested you feel. They are unrelated to waking up from a bad dream or your partner tossing and turning. Instead, they seem to be linked to some internal biological mechanism.

Frequently waking up throughout the night may have protected early humans from predators by increasing their awareness of their surroundings during sleep. "The likelihood someone would notice an animal is higher [if they] wake up more often," says Ronny Bartsch, a physicist at Bar-Ilan University in Israel. "When you wake up, you're more prone to hear things. In deep sleep, you're completely isolated."

Sleep scientists, however, have been stumped as to what triggers these nocturnal disruptions. In a new *Science Advances* paper Bartsch proposes an innovative hypothesis that spontaneous arousals are due to random electrical activity in a specific set of neurons in the brain—aptly named the wake-promoting neurons.

Even when you are asleep your brain

cells continuously buzz with a low level of electrical activity akin to white noise on the radio. Occasionally, this electrical clamor reaches a threshold that triggers the firing of neurons. The new paper suggests that when random firing occurs in the wake-promoting neurons, a person briefly jerks awake. But this is countered by a suite of sleep-promoting neurons that helps one quickly fall back to sleep.

Low-level electrical activity in neurons increases in colder temperatures whereas warmer temperatures flatten it. As a result, there should be fewer spontaneous arousals in hot weather. To test this theory, the researchers created computer models that mapped how neuronal noise should act at different temperatures and how the varying electrical activity could affect spontaneous arousals. They also measured sleep in zebra fish, which have similar day/night cycles to humans but are ectothermic, meaning their body temperature is controlled by the environment rather than by internal processes.

The researchers compared the fish's sleep rates at four different water temperatures: 77, 82 (ideal for zebra fish), 84 and 93 degrees Fahrenheit. Across the board,

the colder the water the more often the zebra fish woke up and the longer they stayed awake. The data from the zebra fish and the models of temperature, neuronal noise and arousal matched perfectly. "I think their theory is a perfectly good one and may even be correct," says Clifford Saper, a neuroscientist at Harvard Medical School's Division of Sleep Medicine and head of neurology at Beth Israel Deaconess Medical Center who was not involved with the study. "But the experiment they did doesn't test that hypothesis."

The zebra fish experiment shows the fish wake up more frequently and stay awake for longer in colder temperatures but reveals nothing about these animals' neuronal noise—or humans', for that matter. Bartsch says that, so far, no studies have figured out how to measure neuronal noise in a sleeping animal.

The idea that warm temperatures cause fewer nocturnal disruptions also seemingly flies in the face of conventional wisdom that a colder bedroom leads to better sleep. But waking up because you are hot and uncomfortable is different from these brief spontaneous arousals. In fact, our bodies are pretty good at regulating their core

brain and body temperatures, so the difference of a few degrees outside would not alter neuronal activity. In contrast, zebra fish's temperature varies quite a bit. Saper says because of this zebra fish "are probably the last animal that I would use to try to make this point."

Bartsch emphasizes the study is not trying to make a claim about thermoregulation in adults but he says it may have implications for newborn babies. "Because very young infants are more ectothermic than endothermic, their arousability could scale similarly to fish for different ambient temperatures."

Infants are not as good at regulating their own temperature and so are more vulnerable to changes in the environment. (This is why premature babies have to be kept in incubators.) Consequently, the researchers think newborns may be more susceptible to heat-related fluctuations in neuronal noise.

The theory may have important implications for infant sleep. Although they may be disruptive to parents, spontaneous arousals could help save a baby's life. Sudden infant death syndrome (SIDS) has been a leading cause of mortality in children be-

Infants are not as good at regulating their own temperature and so are more vulnerable to changes in the environment.

tween one month and one year of age and yet largely remains a mystery. One idea is that SIDS is caused by a stoppage in breathing, often through accidental suffocation. Waking up during the night can prompt babies to shift or cry out, helping to ensure that they do not have anything obstructing their airways and are still breathing. "We came up again with a theory that the babies with SIDS have low neuronal noise and therefore they have lower arousals," says Hila Dvir, a physicist at Bar-Ilan University who co-authored the paper. "Because they have low arousals, they are less protected from any hypoxic event—a shortage of oxygen."

Not everyone is convinced, though. "Over the years, people have come up with ideas to explain SIDS, like a single explanation for it, and they just keep hitting

dead ends with it because it's probably a complex, heterogeneous situation," says Rafael Pelayo, a clinical professor at the Stanford Center for Sleep Sciences and Medicine. "It is a cool idea that this neuronal noise is explaining the arousals. I just think they jumped a little bit when they got into SIDS. It has to be more complicated than that."

— DANA G. SMITH



10 Things You Don't Know about Yourself

You probably do not
understand yourself as well
as you think you do

By Steve Ayan

1. Your perspective on yourself is distorted.

Your “self” lies before you like an open book. Just peer inside and read: who you are, your likes and dislikes, your hopes and fears; they are all there, ready to be understood. This notion is popular but is probably completely false! Psychological research shows that we do not have privileged access to who we are. When we try to assess ourselves accurately, we are really poking around in a fog.

Princeton University psychologist Emily Pronin, who specializes in human self-perception and decision making, calls the mistaken belief in privileged access the “introspection illusion.” The way we view ourselves is distorted, but we do not realize it. As a result, our self-image has surprisingly little to do with our actions. For example, we may be absolutely convinced that we are empathetic and generous but still walk right past a homeless person on a cold day.

The reason for this distorted view is

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quite simple, according to Pronin. Because we do not *want* to be stingy, arrogant or self-righteous, we assume that we are not any of those things. As evidence, she points to our divergent views of ourselves and others. We have no trouble recognizing how prejudiced or unfair our office colleague acts toward another person. But we do not consider that we could behave in much the same way: because we *intend* to be morally good, it never occurs to us that we, too, might be prejudiced.

Pronin assessed her thesis in a number of experiments. Among other things, she had her study participants complete a test involving matching faces with personal statements that would supposedly assess their social intelligence. Afterward, some of them were told that they had failed and were asked to name weaknesses in the testing procedure. Although the opinions of the subjects were almost certainly biased (not only had they supposedly failed the test, they were also being asked to critique it), most of the participants said their evaluations were completely objective. It was much the same in judging works of art, al-

though subjects who used a biased strategy for assessing the quality of paintings nonetheless believed that their own judgment was balanced. Pronin argues that we are primed to mask our own biases.

Is the word “introspection” merely a nice metaphor? Could it be that we are not really looking into ourselves, as the Latin root of the word suggests, but producing a flattering self-image that denies the failings that we all have? The research on self-knowledge has yielded much evidence for this conclusion. Although we think we are observing ourselves clearly, our self-image is affected by processes that remain unconscious.

2. Your motives are often a complete mystery to you.

How well do people know themselves? In answering this question, researchers encounter the following problem: to assess a person’s self-image, one would have to know who that person is. Investigators use a variety of techniques to tackle such questions. For example, they compare the self-assessments of test subjects with the

subjects' behavior in laboratory situations or in everyday life. They may ask other people, such as relatives or friends, to assess subjects as well. And they probe unconscious inclinations using special methods.

To measure unconscious inclinations, psychologists can apply a method known as the implicit association test (IAT), developed in the 1990s by Anthony Greenwald of the University of Washington and his colleagues, to uncover hidden attitudes. Since then, numerous variants have been devised to examine anxiety, impulsiveness and sociability, among other features. The approach assumes that instantaneous reactions require no reflection; as a result, unconscious parts of the personality come to the fore.

Notably, experimenters seek to determine how closely words that are relevant to a person are linked to certain concepts. For example, participants in a study were asked to press a key as quickly as possible when a word that described a characteristic such as extroversion (say, “talkative” or “energetic”) appeared on a screen. They were also asked to press the same key as



Insecure? Who, me?! We often understand only poorly the effect we have on others.

soon as they saw a word on the screen that related to themselves (such as their own name). They were to press a different key as soon as an introverted characteristic (say, “quiet” or “withdrawn”) appeared or when the word involved someone else. Of course, the words and key combinations

were switched over the course of many test runs. If a reaction was quicker when a word associated with the participant followed “extroverted,” for instance, it was assumed that extroversion was probably integral to that person’s self-image.

Such “implicit” self-concepts generally

correspond only weakly to assessments of the self that are obtained through questionnaires. The image that people convey in surveys has little to do with their lightning-fast reactions to emotionally laden words. And a person's implicit self-image is often quite predictive of his or her actual behavior, especially when nervousness or sociability is involved. On the other hand, questionnaires yield better information about such traits as conscientiousness or openness to new experiences. Psychologist Mitja Back of the University of Münster in Germany explains that methods designed to elicit automatic reactions reflect the spontaneous or habitual components of our personality. Conscientiousness and curiosity, on the other hand, require a certain degree of thought and can therefore be assessed more easily through self-reflection.

3. Outward appearances tell people a lot about you.

Much research indicates that our nearest and dearest often see us better than we see ourselves. As psychologist Simine Vazire of the University of California, Davis, has

shown, two conditions in particular may enable others to recognize who we really are most readily: First, when they are able to “read” a trait from outward characteristics and, second, when a trait has a clear positive or negative valence (intelligence and creativity are obviously desirable, for instance; dishonesty and egocentricity are not). Our assessments of ourselves most closely match assessments by others when it comes to more neutral characteristics.

The characteristics generally most readable by others are those that strongly affect our behavior. For example, people who are naturally sociable typically like to talk and seek out company; insecurity often manifests in behaviors such as hand-wringing or averting one's gaze. In contrast, brooding is generally internal, unspooling within the confines of one's mind.

We are frequently blind to the effect we have on others because we simply do not see our own facial expressions, gestures and body language. I am hardly aware that my blinking eyes indicate stress or that the slump in my posture betrays how heavily something weighs on me. Because it is so

difficult to observe ourselves, we must rely on the observations of others, especially those who know us well. It is hard to know who we are unless others let us know how we affect them.

4. Gaining some distance can help you know yourself better.

Keeping a diary, pausing for self-reflection and having probing conversations with others have a long tradition, but whether these methods enable us to know ourselves is hard to tell. In fact, sometimes doing the opposite—such as letting go—is more helpful because it provides some distance. In 2013 Erika Carlson, now at the University of Toronto, reviewed the literature on whether and how mindfulness meditation improves one's self-knowledge. It helps, she noted, by overcoming two big hurdles: distorted thinking and ego protection. The practice of mindfulness teaches us to allow our thoughts to simply drift by and to identify with them as little as possible. Thoughts, after all, are “only thoughts” and not the absolute truth. Frequently, stepping out of oneself in this way and simply observing



what the mind does fosters clarity.

Gaining insight into our unconscious motives can enhance emotional well-being. Oliver C. Schultheiss of Friedrich-Alexander University of Erlangen-Nürnberg in Germany has shown that our sense

of well-being tends to grow as our conscious goals and unconscious motives become more aligned or congruent. For example, we should not slave away at a career that gives us money and power if these goals are of little importance to us. But how

Self-discovery by diary? Those who view themselves at a distance from their self—for example, in solitude—may see themselves more clearly.

do we achieve such harmony? By imagining, for example. Try to imagine, as vividly and in as much detail as possible, how things would be if your most fervent wish came true. Would it really make you happier? Often we succumb to the temptation to aim excessively high without taking into account all of the steps and effort necessary to achieve ambitious goals.

5. We too often think we are better at something than we are.

Are you familiar with the Dunning Kruger effect? It holds that the more incompetent people are, the less they are aware of their incompetence. The effect is named after David Dunning of the University of Michigan and Justin Kruger of New York University.

Dunning and Kruger gave their test subjects a series of cognitive tasks and asked them to estimate how well they did. At best, 25 percent of the participants viewed their performance more or less realistically; only

some people underestimated themselves. The quarter of subjects who scored worst on the tests *really* missed the mark, wildly exaggerating their cognitive abilities. Is it possible that boasting and failing are two sides of the same coin?

As the researchers emphasize, their work highlights a general feature of self-perception: each of us tends to overlook our cognitive deficiencies. According to psychologist Adrian Furnham of University College London, the statistical correlation between perceived and actual IQ is, on average, only 0.16—a pretty poor showing, to put it mildly. By comparison, the correlation between height and sex is about 0.7.

So why is the chasm between would-be and actual performance so gaping? Don't we all have an interest in assessing ourselves realistically? It surely would spare us a great deal of wasted effort and perhaps a few embarrassments. The answer, it seems, is that a moderate inflation of self-esteem has certain benefits. According to a review by psychologists Shelley Taylor of the University of California, Los Angeles, and Jonathon Brown of the University of Washing-

ton, rose-colored glasses tend to increase our sense of well-being and our performance. People afflicted by depression, on the other hand, are inclined to be brutally realistic in their self-assessments. An embellished self-image seems to help us weather the ups and downs of daily life.

6. People who tear themselves down experience setbacks more frequently.

Although most of our contemporaries harbor excessively positive views of their honesty or intelligence, some people suffer from the opposite distortion: they belittle themselves and their efforts. Experiencing contempt and belittlement in childhood, often associated with violence and abuse, can trigger this kind of negativity—which, in turn, can limit what people can accomplish, leading to distrust, despair and even suicidal thoughts.

It might seem logical to think that people with a negative self-image would be just the ones who would want to overcompensate. Yet as psychologists working with William Swann of the University of Texas at Austin discovered, many individuals

racked with self-doubt seek confirmation of their distorted self-perception. Swann described this phenomenon in a study on contentment in marriage. He asked couples about their own strengths and weaknesses, the ways they felt supported and valued by their partner, and how content they were in the marriage. As expected, those who had a more positive attitude toward themselves found greater satisfaction in their relationship the more they received praise and recognition from their other half. But those who habitually picked at themselves felt safer in their marriage when their partner reflected their negative image back to them. They did not ask for respect or appreciation. On the contrary, they wanted to hear exactly their own view of themselves: “You're incompetent.”

Swann based his theory of self-verification on these findings. The theory holds that we want others to see us the way we see ourselves. In some cases, people actually provoke others to respond negatively to them so as to prove how worthless they are. This behavior is not necessarily masochism. It is symptomatic of the desire for

coherence: if others respond to us in a way that confirms our self-image, then the world is as it should be.

Likewise, people who consider themselves failures will go out of their way *not* to succeed, contributing actively to their own undoing. They will miss meetings, habitually neglect doing assigned work and get into hot water with the boss. Swann's approach contradicts Dunning and Kruger's theory of overestimation. But both camps are probably right: hyperinflated egos are certainly common, but negative self-images are not uncommon.

7. You deceive yourself without realizing it.

According to one influential theory, our tendency for self-deception stems from our desire to impress others. To appear convincing, we ourselves must be convinced of our capabilities and truthfulness. Supporting this theory is the observation that successful manipulators are often quite full of themselves. Good salespeople, for example, exude an enthusiasm that is contagious; conversely, those who doubt them-



selves generally are not good at sweet talking. Lab research is supportive as well. In one study, participants were offered money if, in an interview, they could convincingly claim to have aced an IQ test. The more effort the candidates put into their performance, the more they themselves came to believe that they had a high IQ, even though their actual scores were more or less average.

Our self-deceptions have been shown to be quite changeable. Often we adapt them

Buddhists believe that the ego is an illusion. Research shows, however, that this belief fosters a greater fear of death than believing in a true self does.

flexibly to new situations. This adaptability was demonstrated by Steven A. Sloman of Brown University and his colleagues. Their subjects were asked to move a cursor to a dot on a computer screen as quickly as possible. If the participants were told that above-average skill in this task reflected high intelligence, they immediately concentrated on the task and did better. They

did not actually seem to think that they had exerted more effort—which the researchers interpret as evidence of a successful self-deception. On the other hand, if the test subjects were convinced that only dimwits performed well on such stupid tasks, their performance tanked precipitously.

But is self-deception even possible? Can we know something about ourselves on some level without being conscious of it? Absolutely! The experimental evidence involves the following research design: Subjects are played audiotapes of human voices, including their own, and are asked to signal whether they hear themselves. The recognition rate fluctuates depending on the clarity of the audiotapes and the loudness of the background noise. If brain waves are measured at the same time, particular signals in the reading indicate with certainty whether the participants heard their own voice.

Most people are somewhat embarrassed to hear their own voice. In a classic study, Ruben Gur of the University of Pennsylvania and Harold Sackeim of Columbia University made use of this reticence, compar-

But is self-deception even possible? Can we know something about ourselves on some level without being conscious of it?

ing the statements of test subjects with their brain activity. Lo and behold, the activity frequently signaled, “That’s me!” without subjects’ having overtly identified a voice as their own. Moreover, if the investigators threatened the participants’ self-image—say, by telling them that they had scored miserably on another (irrelevant) test—they were even less apt to recognize their voice. Either way, their brain waves told the real story.

In a more recent study, researchers evaluated performances on a practice test meant to help students assess their own knowledge so that they could fill in gaps. Here subjects were asked to complete as many tasks as possible within a set time limit. Given that the purpose of the prac-

tice test was to provide students with information they needed, it made little sense for them to cheat; on the contrary, artificially pumped-up scores could have led them to let their studies slide. Those who tried to improve their scores by using time beyond the allotted completion period would just be hurting themselves.

But many of the volunteers did precisely that. Unconsciously, they simply wanted to look good. Thus, the cheaters explained their running over time by claiming to have been distracted and wanting to make up for lost seconds. Or they said that their fudged outcomes were closer to their “true potential.” Such explanations, according to the researchers, confuse cause and effect, with people incorrectly



thinking, “Intelligent people usually do better on tests. So if I manipulate my test score by simply taking a little more time than allowed, I’m one of the smart ones, too.” Conversely, people performed less diligently if they were told that doing well indicated a higher risk for developing schizophrenia. Researchers call this phenomenon diagnostic self-deception.

8. The “true self” is good for you.

Most people believe that they have a solid essential core, a true self. Who they truly are is evinced primarily in their moral values and is relatively stable; other preferences may change, but the true self remains the same. Rebecca Schlegel and Joshua Hicks, both at Texas A&M University, and their colleagues have examined how peo-

People who are unsure of their own generosity often donate more to good causes.

ple’s view of their true self affects their satisfaction with themselves. The researchers asked test subjects to keep a diary about their everyday life. The participants turned out to feel most alienated from themselves when they had done something morally questionable: they felt especially unsure of who they actually were when they had been dishonest or selfish. Experiments have also confirmed an association between the self and morality. When test subjects are reminded of earlier wrongdoing, their surety about themselves takes a hit.

George Newman and Joshua Knobe, both at Yale University, have found that people typically think humans harbor a true self that is virtuous. They presented subjects with case studies of dishonest people, racists, and the like. Participants generally attributed the behavior in the case studies to environmental factors such as a difficult childhood—the real essence of these people must surely have been different. This work shows our tendency to think that, in

their heart of hearts, people pull for what is moral and good.

Another study by Newman and Knobe involved “Mark,” a devout Christian who was nonetheless attracted to other men. The researchers sought to understand how the participants viewed Mark’s dilemma. For conservative test subjects, Mark’s “true self” was not gay; they recommended that he resist such temptations. Those with a more liberal outlook thought he should come out of the closet. Yet if Mark was presented as a secular humanist who thought being homosexual was fine but had negative feelings when thinking about same-sex couples, the conservatives quickly identified this reluctance as evidence of Mark’s true self; liberals viewed it as evidence of a lack of insight or sophistication. In other words, what we claim to be the core of another person’s personality is in fact rooted in the values that we ourselves hold most dear. The “true self” turns out to be a moral yardstick.

The belief that the true self is moral probably explains why people connect personal improvements more than personal

Prospective Buddhist monks are taught to see through the illusionary character of the ego—it is always in flux and completely malleable.

deficiencies to their “true self.” Apparently we do so actively to enhance appraisals of ourselves. Anne E. Wilson of Wilfrid Laurier University in Ontario and Michael Ross of the University of Waterloo in Ontario have demonstrated in several studies that we tend to ascribe more negative traits to the person we were in the past—which makes us look better in the here and now. According to Wilson and Ross, the further back people go, the more negative their characterization becomes. Although improvement and change are part of the normal maturation process, it feels good to believe that over time, one has become “who one really is.”

Assuming that we have a solid core identity reduces the complexity of a world that

is constantly in flux. The people around us play many different roles, acting inconsistently and at the same time continuing to develop. It is reassuring to think that our friends Tom and Sarah will be precisely the same tomorrow as they are today and that they are basically good people—regardless of whether that perception is correct.

Is life without belief in a true self even imaginable? Researchers have examined this question by comparing different cultures. The belief in a true self is widespread in most parts of the world. One exception is Buddhism, which preaches the nonexistence of a stable self. Prospective Buddhist monks are taught to see through the illusionary character of the ego—it is always in flux and completely malleable.

Nina Strohminger of the University of Pennsylvania and her colleagues wanted to know how this perspective affects the fear of death of those who hold it. They gave a series of questionnaires and scenarios to about 200 lay Tibetans and 60 Buddhist monks. They compared the results with those of Christians and nonreligious people in the U.S., as well as with those of Hindus (who, much like Christians, believe that a core of the soul, or *atman*, gives human beings their identity). The common image of Buddhists is that they are deeply relaxed, completely “selfless” people. Yet the less that the Tibetan monks believed in a stable inner essence, the more likely they were to fear death. In addition, they were significantly more selfish in a hypothetical scenario in which forgoing a particular medication could prolong the life of another person. Nearly three out of four monks decided against that fictitious option, far more than the Americans or Hindus. Self-serving, fearful Buddhists? In another paper, Strohminger and her colleagues called the idea of the true self a “hopeful phantasm,” albeit a

possibly useful one. It is, in any case, one that is hard to shake.

9. Insecure people tend to behave more morally.

Insecurity is generally thought of as a drawback, but it is not entirely bad. People who feel insecure about whether they have some positive trait tend to try to prove that they do have it. Those who are unsure of their generosity, for example, are more likely to donate money to a good cause. This behavior can be elicited experimentally by giving subjects negative feedback—for instance, “According to our tests, you are less helpful and cooperative than average.” People dislike hearing such judgments and end up feeding the donation box.

Drazen Prelec, a psychologist at the Massachusetts Institute of Technology, explains such findings with his theory of self-signaling: what a particular action says about me is often more important than the action’s actual objective. More than a few people have stuck with a diet because they did not want to appear weak-willed. Conversely, it has been empirically established that those

who are sure that they are generous, intelligent or sociable make less effort to prove it. Too much self-assurance makes people complacent and increases the chasm between the self that they imagine and the self that is real. Therefore, those who think they know themselves well are particularly apt to know themselves less well than they think.

10. If you think of yourself as flexible, you will do much better.

People’s own theories about who they are influence how they behave. One’s self-image can therefore easily become a self-fulfilling prophecy. Carol Dweck of Stanford University has spent much time researching such effects. Her takeaway: if we view a characteristic as mutable, we are inclined to work on it more. On the other hand, if we view a trait such as IQ or willpower as largely unchangeable and inherent, we will do little to improve it.

In Dweck’s studies of students, men and women, parents and teachers, she gleaned a basic principle: people with a rigid sense of self take failure badly. They see it as evidence of their limitations and fear it; fear

of failure, meanwhile, can itself cause failure. In contrast, those who understand that a particular talent can be developed accept setbacks as an invitation to do better next time. Dweck thus recommends an attitude aimed at personal growth. When in doubt, we should assume that we have something more to learn and that we can improve and develop.

But even people who have a rigid sense of self are not fixed in all aspects of their personality. According to psychologist Andreas Steimer of the University of Heidelberg in Germany, even when people describe their strengths as completely stable, they tend to believe that they will outgrow their weaknesses sooner or later. If we try to imagine how our personality will look in several years, we lean toward views such as: “Level-headedness and clear focus will still be part and parcel of who I am, and I’ll probably have fewer self-doubts.”

Overall, we tend to view our character as more static than it is, presumably because this assessment offers security and direction. We want to recognize our particular traits and preferences so that we can act

accordingly. In the final analysis, the image that we create of ourselves is a kind of safe haven in an ever-changing world.

And the moral of the story? According to researchers, self-knowledge is even more difficult to attain than has been thought. Contemporary psychology has fundamentally questioned the notion that we can know ourselves objectively and with finality. It has made it clear that the self is not a “thing” but rather a process of continual adaptation to changing circumstances. And the fact that we so often see ourselves as more competent, moral and stable than we actually are serves our ability to adapt. **M**

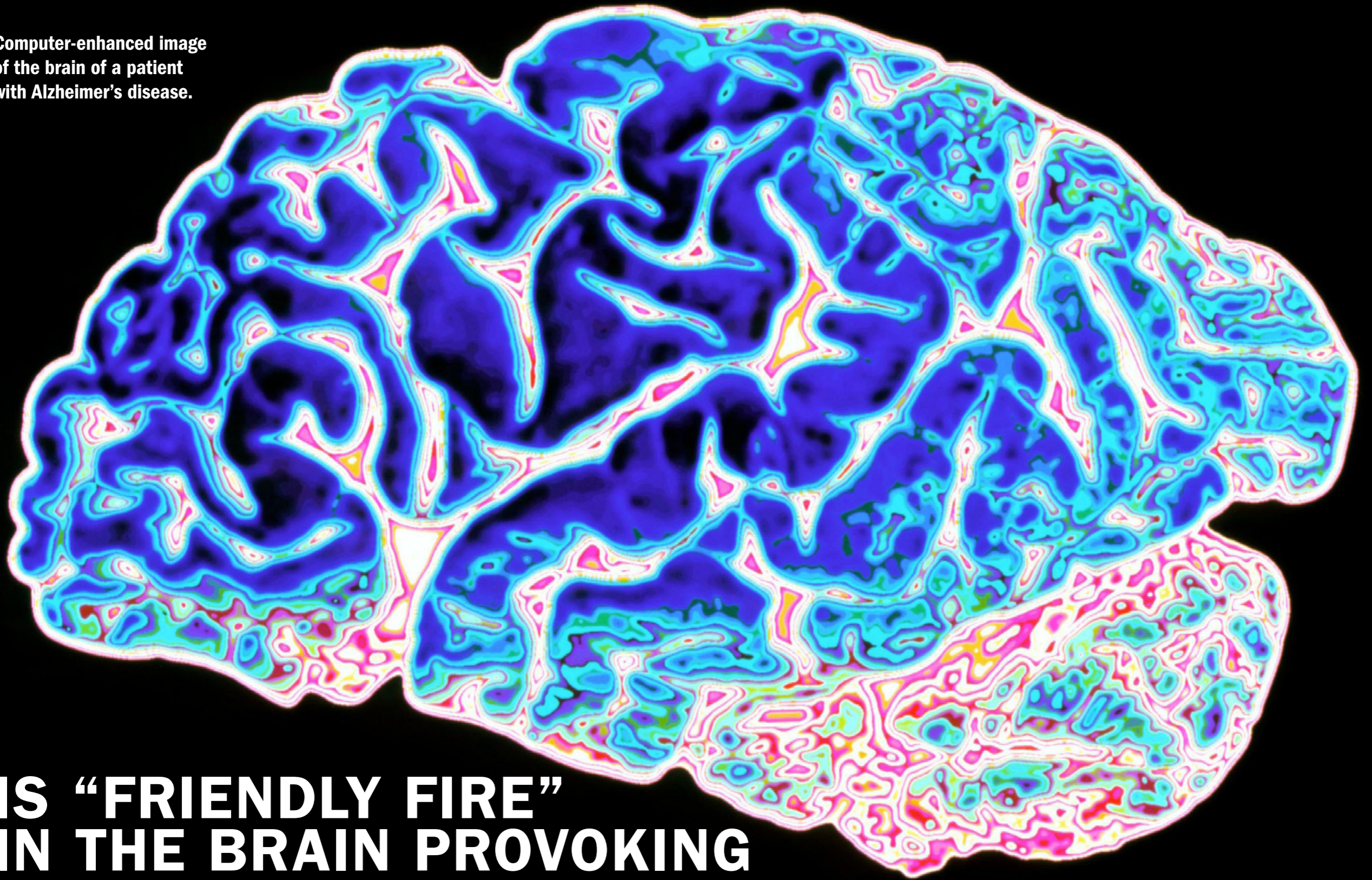
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Computer-enhanced image
of the brain of a patient
with Alzheimer's disease.



IS “FRIENDLY FIRE” IN THE BRAIN PROVOKING ALZHEIMER’S DISEASE?

Scientists want to combat dementia and neurodegeneration
by keeping the brain’s immune system from going rogue

By Alison Abbott

Neuroscientist Michael Heneka knows that radical ideas require convincing data. In 2010, very few colleagues shared his belief that the brain's immune system has a crucial role in dementia. So in May of that year, when a batch of new results provided the strongest evidence he had yet seen for his theory, he wanted to be excited, but instead felt nervous.

He and his team had eliminated a key inflammation gene from a strain of mouse that usually develops symptoms of Alzheimer's disease. The modified mice seemed perfectly healthy. They sailed through memory tests and showed barely a sign of the sticky protein plaques that are a hallmark of the disease. Yet Heneka knew that his colleagues would consider the results too good to be true.

Even he was surprised how well the mice fared; he had expected that removal of the gene, known as *Nlpr3*, would protect their brains a little, but not that it would come close to preventing dementia symptoms. "I thought something must have gone wrong

Alison Abbott works for *Nature* magazine.

Scientists don't yet agree on whether the immune system will need to be ramped up or tamped down at different stages of disease.

with the experiments," says Heneka, from the German Center for Neurodegenerative Diseases in Bonn.

He reanalysed the results again and again. It was past midnight when he finally conceded that they might actually be true.

Over the next couple of years, he confirmed that nothing had gone wrong with the experiments. Together with his colleagues, he replicated and elaborated on the results. Since then, numerous studies have bolstered the link between dementia and the brain's immune system, highlighting the cells and signals involved. But none has managed to fully pin it down—the link seems to be slippery and dynamic, changing as the disease progresses.

Even so, the idea has sparked the interest of pharmaceutical investors, who see a large, and entirely unserved, market: an es-

timated 50 million people worldwide have dementia—a number the World Health Organization projects will rise to 82 million by 2030. Of the eight drug-discovery projects backed by Dementia Consortium—a UK-based group of charities and pharmaceutical companies that has poured £4.5 million (US\$5.7 million) into the projects—four are aimed at inflammation.

But there are roadblocks ahead. Scientists don't yet agree on whether the immune system will need to be ramped up or tamped down at different stages of disease. And some of the practical problems that have dogged clinical trials in Alzheimer's disease—imperfect mouse models and difficulties in recruiting patients early enough—may plague this new approach, too. Hanging over the field like a black cloud is the fact that all clinical trials in

Alzheimer's disease have so far failed.

Still, Martin Hoffman-Apitius, a bioinformatician at the Fraunhofer Institute for Algorithms and Scientific Computing in Sankt Augustin, Germany, who specializes in pharmaceutical research, notes that researchers have filed several patents relating to inflammation-related targets. "Soon we will see a wave of clinical trials," he predicts.

Clogged and Swollen

The German psychiatrist Alois Alzheimer was the first to describe the symptoms and pathology of dementia, in the early twentieth century. Looking under the microscope at the brain of a woman whose cognitive decline he had witnessed, he saw—and neatly drew—the plaques, now known to contain amyloid- β , and tangles of a protein called tau that together are the signature of the disease. In those earliest depictions of the affected brain tissue, Alzheimer also sketched microglia, a type of immune cell in the brain, nestling next to neurons. "Alzheimer himself noticed the cells and drew them in abundant number alongside neurons," says Heneka.

Although the sketches made no deeper

link between microglia and disease, Heneka remembered them as links between inflammation and Alzheimer's began to emerge in the mid-1990s. He had been intrigued by some epidemiological observations showing that people given some anti-inflammatory drugs (to treat rheumatoid arthritis, for instance) seemed to be at a lower risk of developing Alzheimer's disease than the general population. He became encouraged by reports that microglia gather around plaques and areas of brain degeneration, and that inflammatory molecules such as cytokines collect in the cerebrospinal fluid of patients. Most scientists assumed that these observations reflected a passive response to tissue damage. But Heneka always suspected that inflammation could be actively provoking disease.

Microglia have turned out to be central to the link between inflammation and neurodegeneration. The cells have two major functions. They take care of the general health of neurons and their synapses—the junctions between neurons where they communicate with one another. And they patrol the brain, searching for threats and problems. When they detect an infectious or otherwise-aberrant molecule such as

amyloid- β —or debris from damaged cells—they become activated and signal to other microglia to join them in a clean-up effort. Certain microglial proteins gather into large complexes called inflammasomes (a key component of the inflammasome is Heneka's NLRP3 protein), which churn out clean-up signals in the form of activated immune molecules. Inflammasomes usually ebb away once the job is done, but in Alzheimer's they seem to remain activated, continuing to pump out inflammatory molecules yet failing to clean up properly.

In 2013, microglia began to loom large in Alzheimer's disease research. Around the same time that Heneka's paper showed that preventing inflammation staved off Alzheimer's pathology in mice, the *New England Journal of Medicine* published two large studies of gene variants associated with the disease. Both studies linked the risk of developing late-onset Alzheimer's to a gene called *TREM2*, which makes a protein that sits in the membrane of microglial cells.

Neuroscientists started to pay attention. So did immunologists. An interdisciplinary community of neuroimmunologists burgeoned. "Suddenly, huge opportunities opened up," says neuroscientist Michela

Matteoli at the University of Milan, Italy, who now runs a neuroscience programme in the immunology department at the neighbouring Humanitas Institute. At Humanitas, she found a treasure trove of mouse models lacking specific elements of the immune system, which immunologists had never had reason to use for studying brain function. “Many of the tools we need are available,” she says.

Heroes and Villains

How might microglia, which evolved to keep the brain in good order, become a force for the bad in Alzheimer’s? Last year, Heneka and his colleagues published evidence suggesting a plausible mechanism for the switch, at least in their mice. They found that activated microglia discard the remnants of inflammasomes in tiny clumps called specks, and that these specks go on to seed new amyloid- β clusters, spreading the disease across the brain. “A perfect storm,” says Heneka. “Toxic amyloid- β promotes inflammation, which promotes more toxic amyloid- β .”

He is working together with immunologist Eicke Latz, at the University of Bonn, to develop a drug that can stop the inflam-

The German psychiatrist Alois Alzheimer was the first to describe the symptoms and pathology of dementia, in the early twentieth century.

masome from forming. That would allow the microglia to continue their other important roles in the brain’s housekeeping without conscripting other microglia to help clean up. The storm would be kept at bay.

Latz co-founded the start-up IFM Therapeutics in Boston, Massachusetts, in 2016. The company, which was acquired by the pharmaceutical firm Bristol-Myers Squibb last year, already has some candidate drugs that stop inflammasomes from forming, and Latz and Heneka hope to start clinical trials in the next couple of years.

Meanwhile, neuroimmunologists around the world are trying gain a deeper understanding of the biology of microglia, to work out whether there could be other ways to design immune-based therapies for Alzheimer’s and other neuro-degenerative diseases. Some scientists think that the healthy

activities of microglia could be bolstered to clear toxic amyloid- β more efficiently and avoid the storm altogether.

Two studies in mice and post-mortem human brains have shown that the microglia that huddle around plaques in the brain are a very specific subset. They express some genes at higher or lower levels than regular microglia, and those patterns tell an interesting story: the cells seem to be trying to tune up their normal housekeeping duties to combat the plaques. Some of those genes remove safeguards, or ‘check-points’, from the pathways that lead to the cells’ activation. Others are in pathways that sense damage or encourage microglia to engulf defective molecules. In each case, the gene-expression patterns indicate that the microglia are ramping up their housekeeping duties to try to protect the brain.

Mutations in about a dozen of these genes had already been identified as risk factors for Alzheimer's in humans, says Ido Amit, an immunogeneticist at the Weizmann Institute of Science in Rehovot, Israel, who conducted one of the studies looking at the gene-expression patterns.

Amit says that the cells are clearly there for a reason and might therefore be harnessed to help. "The results seemed to be telling us a strong message about the biology of the system," he says. If microglia could be helped to perform their regular functions more efficiently, and kept from any overzealous cleaning efforts, they might help stave off symptoms of the disease rather than worsening its course.

If there were any doubts still lingering about the importance of microglia in mechanisms of dementia—whether they serve as heroes or villains—these papers eliminated them. What's more, microglia could even be primed for activation by inflammation elsewhere in the body. Epidemiological studies have shown that the burden of infection during life increases the risk of cognitive impairment or dementia in later life. And earlier this month, Jonas Neher from the German Center for Neurodegenerative

Diseases in Tübingen and his colleagues showed that provoking inflammation in mice by injecting molecules called lipopolysaccharides (LPS) into their bellies led to persistent changes in gene expression in brain microglia—even though the molecules themselves didn't enter their brains. Low doses of LPS led to increased levels of amyloid- β and plaques; high doses reduced the burden.

Microglia could even be involved in other neurodegenerative diseases, because similar findings have been observed in models of amyotrophic lateral sclerosis (ALS) and Parkinson's disease. And research from Matteoli and others suggests they could be implicated even more widely in brain disorders, such as the rare neurodevelopmental disorder known as Rett syndrome.

Shelter from the Storm

Amit is now discussing with industrial partners how the housekeeping activities of microglia might be boosted. "This would allow us to reactivate our natural defences when damage is out of control," he says.

Others worry that activating more microglia in late stages of the disease might make things worse. "We just don't know

enough about the biology yet," says Oleg Butovsky, a neuroimmunologist at Harvard Medical School in Boston, who led the other study on gene expression in microglia and is developing biomarkers to identify them in the brain at different stages of the disorder. He says it isn't clear whether microglia should be boosted or suppressed, or even whether different tactics could be used at different times during the progression of the disease.

And not all scientists assume that the role of the immune system in neurodegeneration stops with microglia. Neurologist Philip De Jager at Columbia University in New York is developing an Alzheimer's therapy that is based on a microglial target, but says that cells from the rest of the body's immune system, such as T cells, which are present in very low numbers in the brain, might also turn out to be relevant.

Although clinical interest is taking off, there are two stubborn elephants in the room: the mouse models used in Alzheimer's research are a poor proxy for the human condition, and it is difficult to find people who are good candidates for testing new therapies.

Mice with gene mutations that predis-

pose them to Alzheimer's develop some realistic symptoms, but too quickly. That leaves scientists struggling to identify when treatment should be given. "Our models are just too accelerated," says Marco Colonna from Washington University School of Medicine in St. Louis, who has worked extensively on the biology of TREM2. "The field recognizes that the development of a model where amyloid accumulates more naturally is a priority."

It's also a challenge to identify people early enough in the progression of their disease for any experimental drug to have a chance of working. Alzheimer's researchers think that many of the earlier trials failed not because their hypothesis—that amyloid- β and tau are critically involved in the disease—is incorrect, but because the treatment is given too late. Patients are generally recruited to trials only after their plaque burden and neurodegeneration has advanced and the disease is probably irreversible. This could also be one reason why trials of anti-inflammatory drugs such as naproxen or rofecoxib have gone the same way as other potential treatments and shown no benefit in people with Alzheimer's, says Heneka. Biomarkers to identify

people who are in a very early stage of disease are only now becoming available. Even then, the tests are very expensive and cumbersome, involving brain scans and spinal taps. And they still need to be completely validated in practice.

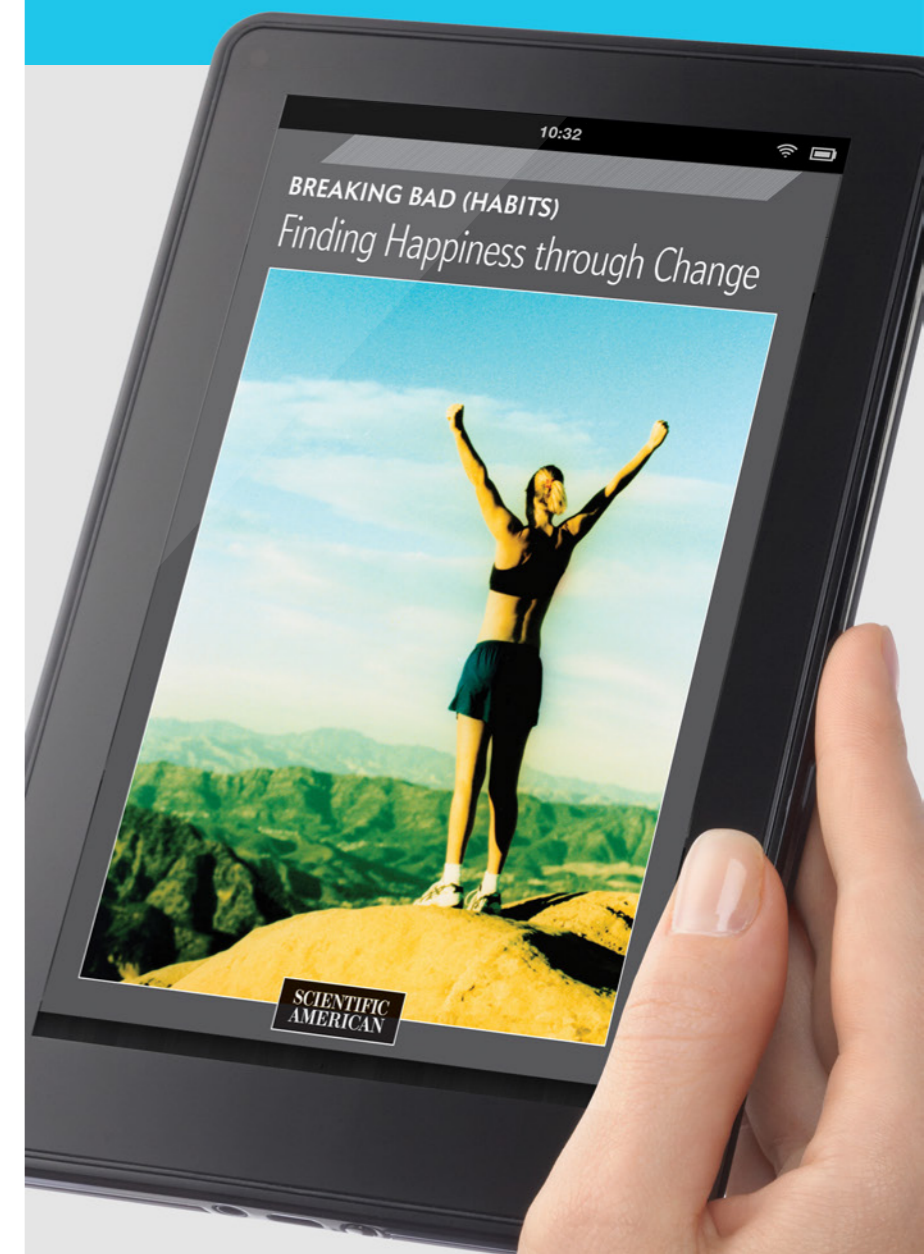
The many uncertainties are not damping enthusiasm. "It's been an exciting few years," says De Jager. Scientists in the field see a parallel with cancer immunotherapy, where the immune system receives a boost to attack tumours. "It seems that diseases not thought classically to be immunological may indeed have an immunological basis."

When Heneka thinks back to his experiments with the unexpectedly smart mice, he is cautiously optimistic that immune-based therapies could work for Alzheimer's disease. But the new trials need to face up to the troubles that plagued previous efforts. No one, he says, wants to see the approach fail for the wrong reasons. Then again, he had never seen a mouse that was supposed to have Alzheimer's pass a memory test with such flying colours.

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Hans Asperger

OPINION

The Truth about Hans Asperger's Nazi Collusion

Neuroscientist Simon Baron-Cohen absorbs the grave revelations in a study on a pediatrician enmeshed in autism's history

By Simon Baron-Cohen

*Asperger's Children:
The Origins of Autism in Nazi Vienna*
by Edith Sheffer. W. W. Norton (2018)

The Austrian paediatrician Hans Asperger has long been recognized as a pioneer in the study of autism. He was even seen as a hero, saving children with the condition from the Nazi killing programme by emphasizing their intelligence. However, it is now indisputable that Asperger collaborated in the murder of children with disabilities under the Third Reich.

Historian Herwig Czech fully documented this in the April 2018 issue of *Molecular Autism* (a journal I co-edit). Now, historian Edith Sheffer's remarkable book *Asperger's Children* builds on Czech's study with her own original scholarship. She makes a compelling case that the foundational ideas of autism emerged in a society that strove for the opposite of neurodiversity.

These findings cast a shadow on the history of autism, already a long struggle to-

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wards accurate diagnosis, societal acceptance and support. The revelations are also causing debate among autistic people, their families, researchers and clinicians over whether the diagnostic label of Asperger's syndrome should be abandoned.

In 1981, psychiatrist Lorna Wing published the paper in *Psychological Medicine* that first brought Asperger's clinical observations to the attention of the English-speaking medical world, and coined the term Asperger's syndrome. A decade later, in the book *Autism and Asperger Syndrome* (1991), developmental psychologist Uta Frith of University College London translated into English the 1944 treatise by Asperger in which he claimed to have discovered autism.

Finally, in 1994, the American Psychiatric Association (APA) recognized the diagnosis of Asperger's syndrome in the fourth edition of its *Diagnostic and Statistical Manual (DSM)*. The syndrome is characterized by strengths such as unusually deep, narrow interests, and challenges in social communication and interaction, in people with average IQ or above and no history of language delay. (In the 2013 revision of the *DSM*, the APA deleted Asperger's syndrome

in favour of a single category, autism spectrum disorder.)

In digging anew into the deeper historical context of Asperger's work, Sheffer fills in parts of the story anticipated in John Donvan and Caren Zucker's history of autism, *In a Different Key* (2016), which referred to Czech's early findings. Sheffer reveals how the Nazi aim of engineering a society they deemed 'pure', by killing people they saw as unworthy of life, led directly to the Holocaust.

With insight and careful historical research, Sheffer uncovers how, under Hitler's regime, psychiatry—previously based on compassion and empathy—became part of an effort to classify the population of Germany, Austria and beyond as 'genetically' fit or unfit. In the context of the 'euthanasia' killing programmes, psychiatrists and other physicians had to determine who would live and who would be murdered. It is in this context that diagnostic labels such as 'autistic psychopathy' (coined by Asperger) were created.

Sheffer lays out the evidence, from sources such as medical records and referral letters, showing that Asperger was complicit in this Nazi killing machine. He protected chil-

dren he deemed intelligent. But he also referred several children to Vienna's Am Spiegelgrund clinic, which he undoubtedly knew was a centre of 'child euthanasia', part of what was later called Aktion T4.

This was where the children whom Nazi practitioners labelled 'genetically inferior' were murdered, because they were seen as incapable of social conformity, or had physical or psychological conditions judged undesirable. Some were starved, others given lethal injections. Their deaths were recorded as due to factors such as pneumonia.

Sheffer argues that Asperger supported the Nazi goal of eliminating children who could not fit in with the *Volk*: the fascist ideal of a homogeneous Aryan people.

Both Czech and Sheffer include details on two unrelated children, Herta Schreiber and Elisabeth Schreiber, and their referral letters, signed by Asperger. In these, the paediatrician justifies Herta's referral to Am Spiegelgrund because she "must be an unbearable burden to the mother"; and Elisabeth's, because "in the family, the child is without a doubt a hardly bearable burden". These provide proof that he effectively signed their death warrants.

Nearly 800 children were killed in Am

Spiegelgrund. Asperger went on to enjoy a long academic career, dying in 1980.

Both *Asperger's Children* and Czech's paper converge on the same conclusion. Personally, I no longer feel comfortable with naming the diagnosis after Hans Asperger. In any case, this is a category rendered moot in the most recent edition of the *DSM* (used in the United States). European nations will follow this diagnostic lead in 2019, with the 11th edition of the *International Classification of Diseases*.

The future use of the term, of course, is a discussion that must incorporate the views of autistic people. Many take pride in the term Asperger's syndrome as part of their identity, feeling it refers to their personality and cognitive style, which obviously do not change simply because of historical revelations. They might not, therefore, want a change. Others have already written about switching to using 'autism' (or autism spectrum disorder, or autism spectrum condition) to describe their diagnosis.

For brevity and neutrality, I favour the single term autism. However, because of the considerable heterogeneity among autistic people, I think it could be helpful for them and their families—together with au-

tism researchers, clinicians and relevant professionals—to discuss whether subtypes should be introduced.

When Wing coined the term Asperger's syndrome, none of us was aware of Hans Asperger's active support of the Nazi programme. As a result of the historical research by Sheffer and Czech, we now need to revise our views, and probably also our language. *Asperger's Children* should be read by any student of psychology, psychiatry or medicine, so that we learn from history and do not repeat its terrifying mistakes. The revelations in this book are a chilling reminder that the highest priority in both clinical research and practice must be compassion.

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OPINION

Why Everyone Is Insecure (and Why That's Okay)

A healthy dose of self-doubt spurs us to monitor ourselves and our interactions and helps us identify how to get along better with our fellow humans

By Ellen Hendriksen

LYNN KOENIG GETTY IMAGES

We all know what it's like to feel as insecure as an e-mail password. We know we should raise our hand in class, but are afraid we'll sound stupid. We pine silently for our crush, but keep our distance so they don't laugh in our face. We want to voice our idea in the meeting, but can't find the words—until we hear someone else say them first.

Call it social anxiety, self-doubt or inhibition. Whatever we call it, it's insecurity, and it's a universal part of the human condition.

This urge to hide starts with the perception that something is wrong with us—we're awkward, annoying, boring, stupid, a big loser, incompetent or any of a million other not-good-enough traits. And we think unless we conceal our perceived flaw, it will become obvious to everyone, who will then judge and reject us.

The mental health profession has even codified insecurity: at some point in life, 13 percent of Americans will cross the line into social anxiety disorder, meaning inse-

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In any organism, from bacteria to fish to modern Americans, behavioral inhibition wires us to look before we leap.

curity that gets in the way of living the life people want to live. We deliberately pass up class participation points. We pass up promotions because they require public speaking. We turn down invitations because we suspect our friends are only including us out of pity.

Furthermore, nearly half of us—40 percent in fact—identify as shy, which is simply the everyday way of saying that insecurity roars to life in social situations where we fear our perceived flaws will be revealed.

And then we kick ourselves: “This is stupid!” “Why can't I do this?” “What is wrong with me?” The answer: nothing. Social anxiety is a disorder precisely because our perceived fatal flaw is just that: a perception.

If it causes all this misery and hand-wringing, why did insecurity stick around through millennia of evolution?

What use does it have? Why didn't it fall away with our tails or get traded for opposable thumbs?

It turns out insecurity isn't an oversight of evolution. In fact, it's necessary: a healthy dose of self-doubt spurs us to monitor ourselves and our interactions. It prompts introspection and helps us identify how to get along better with our fellow humans. In short, we doubt ourselves in order to check ourselves. And those doubts buy us at least three traceable benefits.

First, the biggie: propagation. In 1984, developmental psychologist Cynthia Garcia Coll of Carlos Albizu University in Puerto Rico named the inborn tendency to withdraw from unfamiliar situations, people and environments *behavioral inhibition*. This is our degree of caution when faced with new people, places or events. And it's not just

found in toddlers clinging to mom's leg or cats hiding under the bed when company arrives. In any organism, from bacteria to fish to modern Americans, behavioral inhibition wires us to look before we leap. It's designed to keep us safe and, ultimately, alive, which helps ensure our genes will make it to the next generation.

To further illustrate the importance of behavioral inhibition, let's turn it on its head. What's the opposite of insecurity? Total confidence? Complete fearlessness? At first, that sounds amazing. But be careful what you wish for. Only 1 percent of the population has achieved this dubious goal: psychopaths. Turns out a total lack of insecurity is actually a sign of things gone wrong.

A study by Niels Birbaumer and his team at the University of Tübingen put individuals with social anxiety disorder and criminal psychopaths through an MRI scanner. In those with social anxiety, they found the neural signature of a hair-trigger social smoke alarm: an overactive frontolimbic circuit. In psychopaths, they found the exact opposite: an underactive frontolimbic circuit. Additional studies have strengthened the idea that psychop-

athy and social anxiety lie at opposite ends of the spectrum.

Therefore, in addition to the evolutionary jackpot of reproduction, the second thing insecurity buys us is group harmony. A little insecurity in each of us maintains social cohesion rather than letting rampant psychopaths drag down the whole group. A group that maintains harmony avoids burning its finite time and energy on internal conflict. Over time, a harmonious group will outcompete those weighed down by infighting and power grabs. Indeed, playing well with others is a smarter evolutionary strategy for the group, not to mention all the individuals within it.

And we need a group. Unlike solitary species like tigers or bears, we're social animals, wired to live together. In ancient times, banishment was the worst possible punishment. Being cut off from the group meant certain death, and in some species—chimps, lions and wolves—it still does.

So the third thing insecurity buys us is actual security. Even if online grocery delivery has supplanted our reliance on the group to hunt and gather food, we still need a group for community, belonging and plain old love. A healthy dose of inse-

curity allows us to get along and stay safely in the fold.

There's more: Behavioral inhibition and social anxiety are a package deal. They often come bundled with valuable skills, like conscientiousness, high standards, a strong work ethic, an ability to remember individual faces, empathy and a tendency to work hard at getting along with fellow humans—a skill that's never been more valuable than in today's fractious, divided world.

Therefore, from nature's perspective, it's better to have an overactive social smoke detector. It's better to ring a false alarm when there is no threat than to miss a real threat. False alarms are annoying, but it's much better than the house burning down around us.

Let's wrap it up with a bow and take it home. Insecurity persists because it buys us more than it costs us: self-awareness, safety, group harmony, belonging and a much better life than that of a psychopath. Maybe the shrinking violets and wallflowers of the world are actually the foundation of this beautiful bouquet of humanity. **M**



OPINION

Finland Is the Happiest Country in the World, and Finns Aren't Happy about It

They tend to downplay positive emotions, which could paradoxically increase their satisfaction with life

By Frank Martela

JUHANI SEPPOVAARA GETTY IMAGES

When the *World Happiness Report* announced recently that Finland is the happiest country in the world, we Finns reacted the same way as we have reacted to other top rankings in various international comparisons: we criticized the methodology of the study, questioned its conclusions and pointed to the shortcomings of Finnish society.

It's not the first time something like this has happened. When the World Economic Forum ranked Finland as the most competitive economy in Europe in 2014, the chief executive of the Finnish Chamber of Commerce, Risto Penttilä, felt obliged to write an opinion piece for the *Financial Times* where he tried to prove that the results couldn't be right.

This time it is my duty, as a Finnish expert on well-being research, to explain why the happiness of the Finns has been greatly exaggerated.

More particularly, I'll argue that there are four separate ways to measure happiness—and depending on which one we choose, we

Frank Martela, Ph.D., is a researcher specializing in both the psychology and philosophy of well-being and meaning in life. He is currently based at Aalto University in Finland.

get completely different countries at the top of the rankings. I'll also argue that Finnish people's aversion to happiness might paradoxically make them happier.

So, how did the *World Happiness Report* measure happiness? The study asked people in 156 countries to "value their lives today on a 0 to 10 scale, with the worst possible life as a 0 and the best possible life as a 10." This is a widely used measure of general life satisfaction. And we know that societal factors such as gross domestic product per capita, extensiveness of social services, freedom from oppression, and trust in government and fellow citizens can explain a significant proportion of people's average life satisfaction in a country.

In these measures the Nordic countries—Finland, Sweden, Norway, Denmark, Iceland—tend to score highest in the world. Accordingly, it is no surprise that every time we measure life satisfaction, these countries are consistently in the top 10.

But when you look at how much positive emotion people experience, the top of the world looks very different. Suddenly, Latin American countries such as Paraguay, Guatemala and Costa Rica are the happiest countries on earth. Finland is far from the

top, which should not surprise anybody who is aware of the reputation of Finns as people who don't display their emotions.

Things get even more complicated when we look at the prevalence of depression in different countries. In one comparison made by the World Health Organization, the per capita prevalence of unipolar depressive disorders is highest in the world in the United States. Among Western countries, Finland is number two. Paradoxically then, the same country can be high on both life satisfaction and depression. While there are significant shortcomings in international comparisons of depression and while other research has estimated that the depression rates of Finland would be closer to the global average, what is clear is that Finland is far from the top of the world in preventing depression.

So while Finland might be good at keeping the average life satisfaction levels high, those at risk for depression might not get enough social support to cope with their low mood. Maybe that's why Finland has the highest number of heavy metal bands per capita in the world.

Finally, some people might argue that neither life satisfaction, positive emotions nor absence of depression is enough for

happiness. Instead, something more is required: One has to experience one's life as meaningful. But when Shigehiro Oishi, of the University of Virginia, and Ed Diener, of the University of Illinois at Urbana-Champaign, compared 132 different countries based on whether people felt that their life has an important purpose or meaning, African countries including Togo and Senegal were at the top of the ranking, while the U.S. and Finland were far behind. Here, religiosity might play a role: The wealthier countries tend to be less religious on average, and this might be the reason why people in these countries report less meaningfulness.

What I'm trying to say is that, regarding happiness, it's complicated. Different people define happiness very differently. And the same person or country can be high on one dimension of happiness while being low on another dimension of happiness. Maybe there is no such thing as happiness as such. Instead we should look at these dimensions separately and examine how well various nations are able to support each of them.

Luckily, Finnish people might have one asset regarding happiness: The Finnish tendency to downplay one's own happiness and the norm against too much public display of

joy might actually make Finns happier. This is because social comparison seems to play a significant role in people's life satisfaction. If everybody else is doing better than you, it is hard to be satisfied with your life conditions, no matter how good they objectively are.

This is why researchers are worried that social media, where people are constantly exposed to idealized versions of other people's lives, might make people more depressed. By not displaying, let alone exaggerating, their own happiness, Finns might help each other to make more realistic comparisons, which benefits everybody's happiness.

So, when all is said, is Finland the happiest country in the world or not?

If happiness is the prevalence of positive emotions (let alone the displaying of them), Finland is not the happiest country. If happiness is the absence of depression, Finland is not the happiest country. But if happiness is about a quiet satisfaction with one's life conditions, then Finland, along with other Nordic countries, might very well be the best place to live.

If you prefer to be happy in your own, understated way, then welcome to Finland! **M**

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