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FOR GENERAL INQUIRIES OR TO SEND A LETTER TO THE EDITOR:
Scientific American Mind
415 Madison Avenue
New York NY 10017-1111
212-451-8200
editors@sciammind.com

PHOTOILLUSTRATION BY AARON GOODMAN

Feast, Famine, Freedom

Thoughts of food seem to consume us, weighing heavily on our minds. We hungrily scan the headlines, seeking ways to battle excess pounds. We devour diet advice, to little avail. Despite our good intentions, obesity rates keep climbing. Why is it so hard to stop overeating? "When our stomach begins to growl, too often it drowns out any good advice coming from our brain," writes psychiatrist Oliver Grimm in his article "Addicted to Food?" Any person may have difficulty with restraint at times, as Grimm explains. For binge eaters, the problem intensifies; the brain's reward system can go haywire. In neurobiological terms, binge eating is not dissimilar to drug addiction. Turn to page 36 for details.

At the other end of the food-behavior scale, a person who has, in effect, too much control over what he or she ingests can suffer from self-imposed starvation. People afflicted with disorders such as anorexia eat too little because their distorted mental image of their body looks larger than reality, explain Christian Eggers and Verena Liebers in "Through a Glass, Darkly," which starts on page 30. To return to normal weight, anorexics must learn to adjust their flawed perceptions.

We typically judge "vegetative" patients, who are unresponsive, as being mentally incapable. Are our perceptions misleading us again? In "Freeing a Locked-In Mind," beginning on page 40, staff editor Karen Schrock tells how brain-imaging studies have revealed that some of these patients are, in fact, aware but unable to command their useless body to react. The exciting finding offers hope that we may soon be able to reach at least a number of the 250,000 Americans who have consciousness disorders. In this issue and others, *Scientific American Mind* documents science's efforts to burst such mental shackles—whether behavioral or biological in nature. Stay tuned.

Mariette DiChristina
Executive Editor
editors@sciam.com

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FEATURES

DEPARTMENTS

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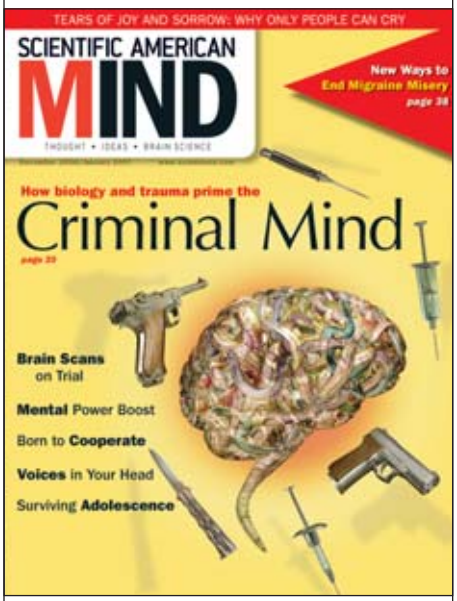


SOCIAL ROOTS OF VIOLENCE

Your coverage of the psychobiological roots of violence in "The Violent Brain," by Daniel Strueber, Monika Lueck and Gerhard Roth, was interesting and compelling. Although their report seems to be accurate, I find problematic the article's near exclusion of a discussion of social factors involved in violence.

Certainly psychobiology can help explain the behaviors of some chronic violent offenders. Yet these extreme cases are rare; it is far more common to find offenders who commit violence as a result of weak bonds to society, goal frustration or other social problems. In fact, the Dunedin study profiled in the article mentions social factors as a likely reason for continued violence among life-course persistent offenders—not psychobiology.

In addition to being misrepresentative, the article's almost total focus on psychobiological roots of violence is only a short step away from a eugenics argument. Considering that 65 percent of U.S. state and federal prisoners in 2005 were nonwhite (according to the Bureau of Justice Statistics), it would be easy for readers to misinterpret this article as promoting the idea that racial and ethnic minorities are "hardwired" to be violent. This potential harm necessitates that research on the psychobiology of violence be discussed within the context of its limited reach and alongside the social causes of violence that criminologists have been promoting for the past century.

Aaron Kupchik
Department of Sociology and Criminal Justice
University of Delaware

SCANNING FOR EVIDENCE

"Brain Scans Go Legal," by Scott T. Grafton, Walter P. Sinnott-Armstrong, Suzanne I. Gazzaniga and Michael S. Gazzaniga, points out the problems involved in using brain scans in criminal cases. But these concerns should not discourage their use for civil cases, in which the standards of proof are significantly lower (that is, "more likely than not" rather than "beyond a reasonable doubt").

An especially important civil application could be determining whether a patient is suffering from pain. HMOs and disability insurers frequently refuse to honor their policies for patients with chronic pain because they say the pain cannot be "objectively demonstrated" and as such is subject to abuse by malingerers and drug seekers. Legitimate patients are thus often denied proper treatment for their symptoms.

Many reports in the literature over the past several years have demonstrated that on a PET or fMRI scan, activation of the somatosensory cortex indicates the sensation of pain and activation of part of the anterior cingulate cortex indicates the emotional aspects of pain. Other reports document that telling a lie activates other regions of the anterior cingulate cortex and, not too surprisingly, parts of the frontal lobe that are connected with creativity.

Such scans might provide the "objective" evidence of pain that insurers desire, while giving them the confidence that they are not paying to treat fakers.

Harvey S. Frey
Santa Monica, Calif.

DEFENDING EMDR

In "Taking a Closer Look" [Facts and Fictions in Mental Health], Scott O. Lilienfeld and Hal Arkowitz give an informative and enthusiastic overview of eye movement desensitization and reprocessing (EMDR). The questions they pose are good ones, but the answers they give deserve some clarification.

The article says, for instance, that EMDR patients must repeatedly visualize the traumatic material, suggesting that EMDR is therefore just another exposure therapy. It is true that at the beginning of treatment, the EMDR subject will target the original traumatic scene, but it is misleading to leave it at that. Unlike exposure therapy, EMDR does not repeatedly return the client's attention to the original event. Rather the flow of experience can lead in many directions: past, present or future; emotional, physical, cognitive or perceptual. The job of the EMDR therapist is to make sure this spontaneous experience occurs freely, without editing, manipulation or interpretation. EMDR reprocessing includes associated feelings and perceptions. Whether to call this adaptation, exposure, desensitization or habituation is not clear.

DAVE NAGEL Getty Images

Is therapy involving eye movements a breakthrough in anxiety disorder treatment?

Several comparison studies and meta-analyses show that EMDR works as well as cognitive and behavioral exposure therapies and better than purely supportive therapies. EMDR has received the imprimatur of the American Psychiatric Association and the Department of Defense and Veterans Affairs for treatment of posttraumatic stress disorder (PTSD).

Although we do not yet know how EMDR works, it is more important that it *does* work. EMDR does not demand that the client describe the event in detail, so it is beneficial to people who cannot—or prefer not to—do so. EMDR does not require learning new skills or habits. In less severe cases, EMDR may require only one or two sessions. Compare this with 30 to 100 hours of homework in cognitively oriented therapies. When cognitive skill and structured activity are important, other trauma therapies may be preferable. But for people who can quickly move into their memories and associations, EMDR may be a better match.

Robert S. Marin
Department of Psychiatry
University of Pittsburgh
School of Medicine

The authors state that EMDR is not more effective than standard behavioral and cognitive-behavioral therapies. I have heard that EMDR is less stressful than standard therapies for PTSD and thus has a lower dropout rate and that this difference is not taken into account in studies of EMDR (because only patients who complete therapy are included in the studies). Is there indeed a difference in dropout rates?

Phil Thompson
Los Altos, Calif.

ARKOWITZ AND LILIENFELD REPLY: *We received many spirited letters raising a variety of intriguing questions concerning the efficacy of EMDR. Yet none present data challenging the central conclusions of our column—namely that EMDR is no more efficacious than behavioral and cognitive-behavioral therapies that rely on exposing clients to anxiety-provoking stimuli and that the eye movements of EMDR do not contribute to its efficacy.*

As Marin notes, EMDR may work better for certain individuals than standard exposure-based treatments, and we encourage research to investigate this possibility. Such data could help us choose whether to use EMDR or traditional exposure for specific clients.

Thompson's letter raises the useful question of whether dropout rates are lower in EMDR than in comparable therapies. A 2004 meta-analysis of 25 studies by Elizabeth A. Hembree of the University of Pennsylvania and her colleagues found no significant differences in dropout between EMDR and other behavioral and cognitive-behavioral therapies.

In our columns, we rely on sound scientific data to shed light on the controversies in mental health. Although personal testimonials and organizational endorsements such as those discussed in several of the letters can be thought-provoking, they do not constitute scientific evidence.

HAPPY MEMORIES

With regard to Mariette DiChristina's From the Editor, I have found a counterexample to our remembering bad things rather than good things. We tend to remember well the very good teachers that we have had, whereas we have to try hard to recover even a sketch of the bad ones. Isn't that a happy and telling exception?

Mark Economos
Scarsdale, N.Y.

Head Lines

TOMEK SIKORA *Getty Images*

On the Other Hand

The good news: as we get older, we become more ambidextrous. The bad news: this new skill develops because the performance of our dominant hand declines so drastically.

Researchers at Ruhr University Bochum in Germany and the California Institute of Technology tested 60 volunteers who described themselves as right-handed. The older the subjects were, the less successful they were at motor performance tests using their dominant hand. Left-hand performance did not deteriorate as drastically with age.

One would think that the dominant hand would resist degeneration better than the other hand, says lead researcher Hubert R. Dinse, a biologist at Ruhr University Bochum. Because the opposite is true, something must cause the decline. Dinse speculates it may come down to simple wear and tear of the hand over time.

In a second experiment that tested hand usage, 36 subjects performed household tasks at home while wearing sensors that detected which hand was in motion at any given time. The sensors indicated that whereas the younger subjects preferred using their dominant hand, the older people used both hands equally—without even knowing it.

"All subjects claimed that they were strict right-handers," says Dinse, probably because they were used to describing themselves that way and because they continued to write with their right hand.

To tease out why these changes take place, Dinse plans to use imaging techniques to compare how cortical activation in the two brain hemispheres changes with age. Previous research has shown that the left hemisphere, which is responsible for the right hand, is more active in young right-handed adults—so aging could induce either a reduction in left hemisphere activation or an enhancement in the right hemisphere.

—Melinda Wenner

Bigger Anesthetics May Be Better

Anesthetics may instigate the same molecular changes in the brain that have been implicated in Alzheimer's disease. After surgery or other procedures requiring anesthesia, some mentally sharp seniors suffer a steep cognitive decline, says Pravat K. Mandal of the University of Pittsburgh. "Nobody knows how it happens." Now he is unraveling exactly how some anesthetics might interact with small proteins or peptides in the brain to cause cognitive problems.

For elderly patients, anesthetics pose a risk.

Although Alzheimer's disease is still not entirely understood, it involves the formation of fibrous protein structures called amyloid plaques in the brain. These plaques occur when so-called amyloid beta peptides begin to clump together. Previous work has shown that mixing anesthetics in a test tube with amyloid beta peptides will result in the peptides sticking together more easily than they otherwise would.

Using a technique called nuclear magnetic resonance (NMR) spectroscopy, Mandal probed the interactions of different anesthetics with amyloid beta peptides. He found that each molecule of an inhaled anesthetic, halothane, binds into a small pocket of the peptide, thereby changing its shape and promoting its clumping with other peptide molecules. Halothane had the greatest clumping effect, yet it is rarely used in North America and Europe. Two other anesthetics—isoflurane and propofol—also cause clumping, but their effect is not as severe. Another one, called thiopental, does not cause clumping at all because its molecule is too big to fit inside the peptide's pocket.

Mandal cautions that these anesthetics and peptides may behave very differently in the brain, so he next plans to look for the same effects in a mouse model of Alzheimer's. If peptide binding is the cause of the cognitive decline, he says, it should be possible to design an anesthetic that binds to the amyloid beta peptide in a way that prevents clumping and so would protect patients during surgery.

—Kurt Kleiner

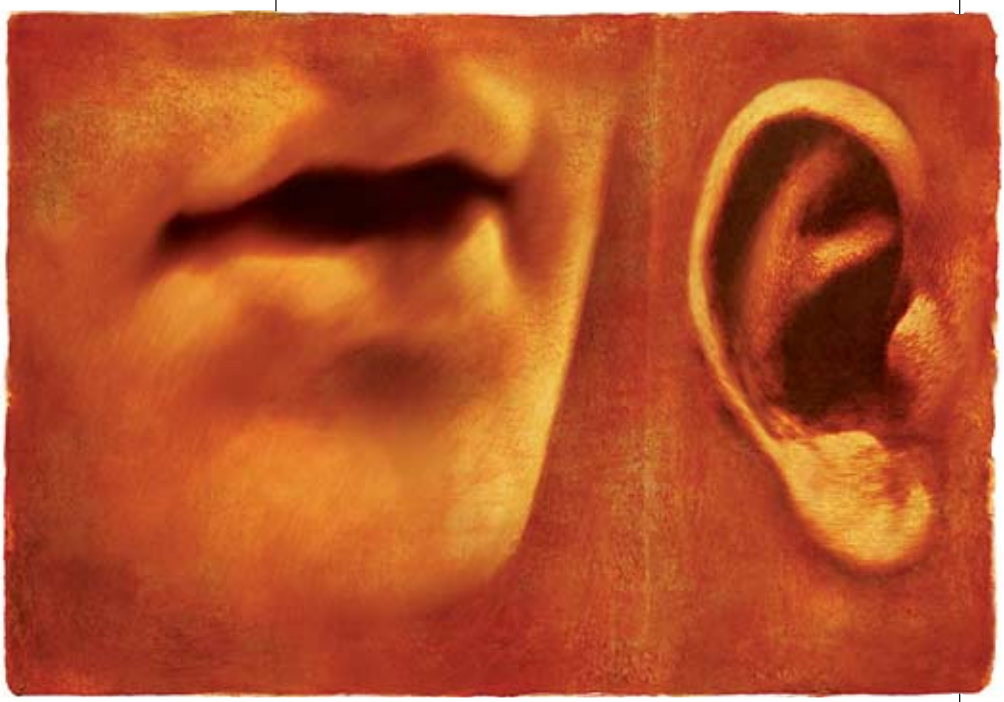
Something, Um, Unexpected

Words like "um" and "er" tend to have a bad reputation, but a new study suggests that they might actually do listeners a favor.

Researchers at the University of Edinburgh and the University of Stirling in the U.K. measured brain activity to assess listeners' understanding. Immediately after a person hears words, brain activity spikes downward. In the study, the larger the spike, the more difficult it was for the listener to put the words into context.

The scientists measured these spikes in 12 people after they heard four combinations of sentences: with either predictable or unpredictable target words at the end and with or without "er" uttered right before the target. They found that an "er"—especially when heard before an unpredictable word—shrunk the brain activity spikes of listeners, suggesting this syllable helped subjects place words in context more easily.

Afterward, the scientists tested the subjects to see which target words they remembered best. "Words that were preceded by this disfluency were more likely to be accurately recognized later," says Martin Corley, a professor at Edinburgh and one of the study's authors. Although the scientists are not sure why the "er" aids listener comprehension and memory, it may warn listeners that something unexpected is coming up. *—Melinda Wenner*



CHARLES THATCHER Getty Images (top); SANDRA BAKER Getty Images (bottom)

Put Your Money Where Your Mind Is

We do not notice many tasks that our brains perform, whereas we are completely aware of others. But it is sometimes hard for neuroscientists to determine when we are conscious of our actions. Now a group of British researchers is betting that betting can be used to study consciousness.

Navindra Persaud, Peter McLeod and Alan Cowey of the University of Oxford were interested in situations in which people can show high levels of cognitive performance with no apparent awareness. In one experiment, they studied a person known as GY, who, because of damage to his visual cortex, reports no vision in his right eye. But GY has a strange ability known as blindsight: he can guess with reasonable accuracy whether or not a symbol is shown to that eye, even though he reports no awareness of seeing it. The question has remained whether at some level he is conscious of his performance.

The researchers asked GY to make one of two wagers after each guess: £1 or half that amount. If he guessed correctly, the sum was added to his winnings. If he guessed incorrectly, the money was subtracted. In other words, GY had a financial incentive to be conscious of when he guessed correctly and bet high on those occasions. But although GY guessed correctly 70 percent of the time, he chose a high wager only about half of the time, almost at random.

The researchers point out that the dissociation between cognitive performance and betting performance is surprising because, in a way, the high and low wagers are a decision very much like GY saying "yes" or "no" to seeing an object. They argue this disconnect between GY's blindsight performance and his betting success suggests that placing a bet is a special type of decision. Successful gambling appears to require consciousness of one's performance.

Persaud and his colleagues have already used this link to measure awareness in healthy volunteers. "We hope to combine [the wager test] with imaging and recording methods," he says. That may make it possible to finally identify the elusive neural circuitry that encodes consciousness.

—Kaspar Mossman

The Prodigal Mind

Our minds are built to wander, according to a new study that argues we have a network of brain regions dedicated to meandering thoughts that turns off and on depending on how focused we need to be to complete different tasks.

Previous studies have shown that this "default" network, which is composed of at least seven separate brain regions, kicks in anytime we are at rest—say, passively taking in a TV show or a sunset. But the function of letting our gray matter go gallivanting has been unclear.

Now Malia F. Mason of Harvard Medical School and her colleagues have found that dull or unchallenging tasks switch on the default network. They scanned the brains of several subjects while their memory of short sequences of letters was being evaluated. When tested on a familiar set of letters that the subjects had been trained on for days—boring!—their daydreaming networks switched into overdrive. But when they had to focus on sorting out new combinations of letters, the networks fell quiet. This pattern matched each person's own reports of when his or her mind wandered from the tasks.

"We're constantly doing things that are pretty mundane," Mason says. She points out that daydreaming is not always frivolous: "Most people say they're planning or thinking about the future, and that's extremely adaptive."

—Mason Inman

CORBIS (*top*); STEPHANIE RAUSSER Getty Images (*bottom*)

Men or women who have been unfaithful to their romantic partners feel better after watching stories about infidelity on television. Robin Nabi of the University of California, Santa Barbara, and her colleagues showed people with a history of cheating two TV programs featuring adultery, one in which the unfaithful spouse expresses regret and one in which the spouse rationalizes the behavior. Whereas the cheaters preferred programs in which the behavior was rationalized, either storyline reduced the viewer's own regret for past indiscretions.

Through the formative ages of four to 13, firstborn children receive 3,000 more hours of quality time with mom and dad than later-born siblings. Joseph Price, a graduate student at Cornell University, made this discovery using data from the American Time Use Survey, by comparing, for example, firstborns in one family with a second-born child of the same age in another. The disparity in parental attention is larger the further apart the siblings are in age. The results suggest that some of the psychological effects attributed to birth order could be driven by the degree of parental involvement.

Quitting smoking is easy for patients with brain damage to the insula, a silver dollar–size region in the cerebral cortex. Researchers at the University of Southern California and the University of Iowa studied a group of 69 stroke patients with brain damage who had been smokers. After their stroke, some patients kicked the habit immediately and easily. Those patients that did not suffer a relapse or a persistent desire to smoke were more likely to have damage to their insula than anywhere else in the brain. The researchers say that drugs targeted to this region may help break cigarette addiction.

Fighting Stress with Stress Hormones

Cortisol, a hormone secreted by the adrenal glands in times of stress, may help people cope when it is given before an unpleasant situation.

Most studies of cortisol have looked at the hormone's negative effects when chronic stress keeps its levels high. Psychologists Oliver T. Wolf and Serkan Het of Bielefeld University in Germany were interested in the short-term effects of cortisol on mood. They gave 22 young women 30 milligrams of cortisol—a fairly high dose. A control group of 22 women received a placebo.

All the subjects were then put in a stressful situation. They were asked to give a speech in a fake job interview and afterward to count backward by 17s from a large number while being monitored by stern-faced examiners and videotaped the whole time. The women were given mood questionnaires before and after their interview.

"The women who got cortisol—compared with those getting placebos—reported less negative effect after the stress test," Wolf says. Exactly how cortisol provided this protection is not clear.

"Cortisol is active in several brain regions that modulate emotions," Wolf explains. "One possibility is that cortisol interferes with retrieving emotional memories, so the subjects weren't able to recall their unpleasant experiences as well." If this is true, he adds, it could point the way toward using cortisol to treat people who have survived terrible events and suffer from posttraumatic stress disorder (PTSD). ***—Jonathan Beard***

Cortisol may interfere with retrieving emotional memories.

ERIN PATRICE O'BRIEN *Getty Images (top)*; GETTY IMAGES *(bottom)*

Being Perfectly Bossy

Would you rather work for an aggressive jerk or a spineless wimp? Unsurprisingly, employees do not like either management style. Instead a good manager has to walk the line between too assertive and not assertive enough.

Social psychologist Daniel R. Ames of Columbia Business School and organizational behavior expert Francis J. Flynn of Stanford University were curious about why previous leadership studies rarely had much to say about assertiveness. It seemed unlikely that assertiveness did not matter. What they found is that assertiveness only seems obvious when you get it wrong. "People don't get credit for getting assertiveness just right. They definitely get criticism when they get it wrong on either side," Ames says.

Ames and Flynn reached the conclusion after surveying business students about the strengths and weaknesses of former colleagues and bosses. Assertiveness was rarely mentioned when listing positive qualities. It tended to show up only on the negatives list and then as one extreme or another.

A boss who is too assertive steps on toes and hurts feelings. Morale among his employees goes down. They do poor work and eventually leave.

But why would an employee complain about a nonassertive boss? The problem is that a boss who is not assertive might not make co-workers pull their weight or might not get the resources his or her team needs to do its job.

Assertiveness matters to more than just a manager's underlings. Both overassertive and underassertive managers are less effective, and over time they are likely to find that their careers are being derailed, Ames says. *—Kurt Kleiner*

The results have implications far beyond sleep disorders.

Tinkering with Our Clock

Inserting a gene that controls human sleep habits into mice can transform the rodents into "early birds." This result provides insight into the molecular mechanisms that drive biological clocks.

Most organisms have an internal clock that synchronizes their activities to the 24-hour day—the so-called circadian rhythm. *PER2* is one of the genes that controls this rhythm in humans. But in 0.3 percent of the population, the gene goes awry, causing familial advanced sleep phase syndrome (FASPS), which drives people early to bed and very early to rise. Despite causing such a striking effect, the change in the protein encoded by the mutant *PER2* gene is quite subtle: a single protein building block, or amino acid, is changed from a serine to a glycine.

To better understand how *PER2* works, Louis J. Ptáček and Ying-Hui Fu of the University of California, San Francisco, genetically engineered mice with the human gene. Sure enough, when the animals received the FASPS *PER2* mutation, their natural rhythm shortened from an average of 23.7 hours to less than 22. When the researchers made another simple amino acid switch in the protein, turning the same serine into an aspartate, the period lengthened to 24.8 hours. Resetting of the mice's clock seemed linked to the activity of the gene. The first mutation lowered gene expression, and the second boosted it.

According to Fu, the results have implications far beyond sleep disorders. Night-shift nurses are more prone to breast cancer, she notes, and chemotherapy is more effective at certain times. Strokes, aneurysms, asthma and depression tend to occur at particular times of day. "Sleep is at the center of all body functions, so understanding circadian rhythm will help us understand related problems," Fu says.

—Karen A. Frenkel

The Medication Munchies Mystery

Antipsychotic drugs have alleviated the debilitating symptoms of thousands of patients with schizophrenia and bipolar disorder, but often at a high price. These drugs can also trigger excessive weight gain, leading to life-threatening complications such as diabetes or heart disease. Now scientists at Johns Hopkins University have uncovered the mechanism by which these drugs stimulate the appetite—a finding that could lead to new agents without the side effect of constant hunger.

Neuroscientists Solomon H. Snyder and Sangwon Kim found that when they administered clozapine, a powerful antipsychotic, to mice, the animals experienced a spike of the appetite-stimulating enzyme AMPK. Then they discovered that blocking a receptor for histamine caused a boost in AMPK similar to the effects of clozapine. Histamine, well known for causing allergy symptoms, has been long suspected to play a role in weight control, but the mechanism has been unknown. The researchers confirmed their finding by administering clozapine to mice genetically engineered to lack the histamine receptor, and these rodents showed no increase in AMPK.

"This is the first time histamine and AMPK have been linked," Kim says. By blocking histamine receptors, clozapine and other antipsychotics prevent cells from receiving the body's signal to turn off AMPK production. As a result, AMPK builds up in the hypothalamus and continues to stimulate appetite, even when enough food has been consumed. He suggests that pharmaceutical companies may be able to screen out antipsychotic drugs with antihistamine properties and thereby avoid the side effects of weight gain. The researchers say their work may also lead to safer weight-loss drugs.

—Karen Schrock

COCOROPHOTOS/CORBIS (*top*); ERIC ANTHONY JOHNSON Getty Images (*bottom*)

Drinking Is No Joke

Alcoholics have trouble understanding jokes, but they may be missing out on much more than a chance to laugh.

German neuroscientists showed 29 alcoholics and 29 healthy control subjects the introduction to a joke and then a choice of punch lines—only one of which made logical sense and was funny. Whereas 92 percent of the nondrinkers chose the correct punch line, only 68 percent of the drinkers did. "The ability to understand jokes is an example of complex social cognition," explains Jennifer Uekermann of Ruhr University Bochum. "It involves detecting incongruity—what's wrong or funny about the story—and putting oneself in another's place."

An alcoholic's problems with social cues are consistent with the "frontal lobe hypothesis," which postulates that damage to the prefrontal cortex—known to be vulnerable to alcohol's toxic effects—leads to behavioral deficits. Most other studies of alcoholics' brain function have concentrated on perceptual problems caused by such damage, Uekermann says. But when a person has deficits in social cognition, he or she has difficulty getting along with and working with other people. A better understanding of how problem drinkers are impaired could help improve rehabilitation programs for alcoholics. ***—Jonathan Beard***

Another Reason to Thank Mom

Maybe it is a good thing we do not remember our births. Difficult ones can be traumatic and a major cause of brain damage. But researchers now suggest that a maternal hormone may protect our brains during birth, providing a natural safeguard against a problematic delivery.

A recent study of pregnant rats, led by Yehezkel Ben-Ari of the Mediterranean Institute of Neurobiology in Marseille, France, examined the effects of the hormone oxytocin. Oxytocin plays well-known roles in bonding between mates, thereby increasing trust among people—and a surge of the hormone can trigger the onset of labor. Ben-Ari's team found that during this same surge, oxytocin latches onto receptors in a fetus's brain. There the hormone acts somewhat like a tranquilizer and lowers the firing rate of a key class of neurons. "I have never seen such a strong inhibition," Ben-Ari says. The effect reaches its peak right before delivery, then wears off in a day.

The tranquilized brain tissue from rat fetuses receiving this hormonal boost resisted damage caused by oxygen deprivation 25 percent longer than tissue from fetuses in which the hormones were blocked. Ben-Ari argues that oxytocin probably works the same way to protect human newborns, because the mechanisms behind this brain shutdown are common to all mammals. *—Mason Inman*

CORBIS (*top*); LWA Getty Images (*bottom*)

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Staving off Dementia

Marijuana's active ingredient may help stall Alzheimer's disease

BY ANDREW KLEIN

MARIJUANA IS INFAMOUS for its ability to muddle thoughts and dull reactions. What is less well known is that it may also blunt the progression of Alzheimer's disease, which relentlessly robs its sufferers of their memories and personality. Families and individuals tormented by this deterioration may welcome such an alternative therapy, no matter how they feel about marijuana's illegal status.

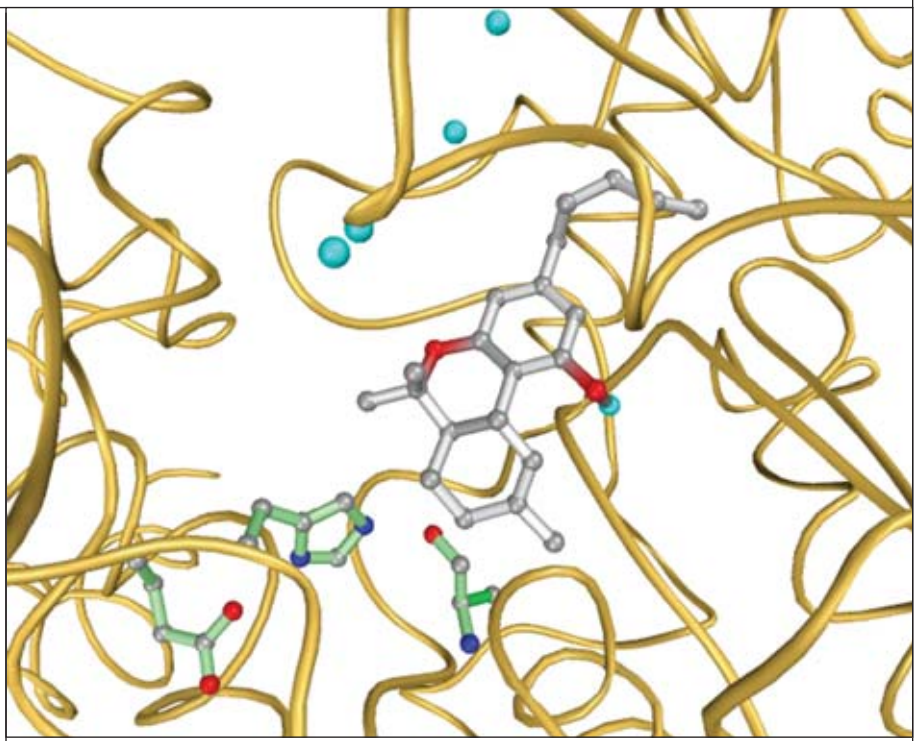
"I went through several years of a son on marijuana and had him placed in a facility to be 'dried out,'" says Ruth, age 69, of St. Louis. Even so, she says she would consider giving the drug to her 79-year-old husband, Joe, who now suffers from Alzheimer's, if it stopped his combativeness and helped to slow his memory loss. Joe is just one of 4.5 million Americans who have the neurodegenerative disorder, which usually strikes after the age of 60 and is found in nearly half of those older than 85.

Several laboratories around the world are now investigating how marijuana may stave off Alzheimer's. It is a new field, and research has not reached clinical testing, but scientists are beginning to understand several biochemical mechanisms by which marijuana may stall the disease—perhaps even more successfully than the most frequently prescribed medications.

Ounce of Prevention

A century ago German doctor Alois Alzheimer first described the disease when he found sticky plaques in the autopsied brains of patients who had exhibited extreme memory loss and confusion. We now know that the senile plaques he observed are composed of beta-amyloid protein and a slew of other toxins, which together form a poisonous gunk that kills cells and causes hemorrhaging. Doctors had no means to treat the disease until 1993, when the Food and Drug Administration approved the cholinesterase inhibitor Cognex, a drug that blocks the enzyme acetylcholinesterase from breaking down acetylcholine, a neurotransmitter that relays signals in the memory areas of the brain.

Plaques produced by Alzheimer's rapidly kill so-called cholinergic neurons, those that synthesize acetylcholine. By raising levels of this neurotransmitter in the brain, Cognex keeps these cells alive longer and slows plaque formation. A newer cholinesterase inhibitor, called Aricept, works in the same way. Research has shown, however, that cholinesterase inhibitors are only moderately effective. In a review of 22 clinical trials, published in the August 6, 2005, edition of the *British Medical Journal*, Hanna Kaduszkiewicz and her colleagues at the University Medical Center Hamburg-Eppendorf in Germany concluded that "because of flawed methods and small clinical benefits, the scientific basis for recommendations of cholinesterase inhibitors for the treatment of Alzheimer's disease is questionable."



Tetrahydrocannabinol (THC, *gray*) binds to acetylcholinesterase (*gold*) and prevents acetylcholine degradation, just as Alzheimer's drugs do.

ALBERT E. BEUSCHER IV

(The **active ingredient** in marijuana binds to the same enzyme targeted by Alzheimer's medications.)

Preventing Alzheimer's at an **early stage** may be the only hope for those at risk.

Many experts believe these drugs simply offer too little too late. By the time a doctor can make a diagnosis and prescribe medication, so many brain cells have been destroyed that boosting the amount of acetylcholine is as futile as tossing a bandage on a massive head wound. Preventing Alzheimer's at an earlier stage may be the only hope for those predisposed to the disease. To that end, new research reveals that the active ingredient in marijuana, tetrahydrocannabinol (THC), may outperform cholinesterase inhibitors. According to Kim D. Janda of the Scripps Research Institute in La Jolla, Calif., THC prevents the degradation of acetylcholine just as Cognex and Aricept do, and it may also hinder toxic proteins from forming plaques.

"We found this mechanism while trying to find a 'vaccine' against pot," Janda says. He has been using computer modeling to study small synthetic molecules he dubs "credit cards" because of their flat shape. THC is a natural "credit card," which enables it to slip between acetylcholine and acetylcholinesterase and impede their interaction. Janda's team reported in the December 2006 issue of *Molecular Pharmaceutics* that the THC molecule binds to a unique location on the acetylcholinesterase enzyme. If you picture the enzyme as a doughnut, Janda explains, Alzheimer's drugs bind to the hole, but THC binds instead to the lip of the hole, blocking the enzyme's actions even more efficiently. "We don't know why it does, it just does," Janda says.

Cannabinoids—the class of drugs to which marijuana belongs—may offer other potential benefits to Alzheimer's patients. According to Maria de Ceballos, a neurology researcher at the Cajal Institute in Madrid, they prevent inflammation caused by overactive microglia and astrocytes, the sanitation workers of the central nervous system. These cells swarm around Alzheimer's plaques and try to rid the brain of the toxins. To do so, however, they secrete additional toxins—nitric oxide and tumor necrosis factor-alpha—that cause swelling and kill neurons.

Microglia and astrocytes sport CB_1 cannabinoid receptors (the same receptors responsible for making people feel "stoned"). According to de Ceballos's research, cannabinoids can plug these receptors, preventing the microglia and astrocytes from producing nitric oxide and tumor necrosis factor-alpha. As with the cholinesterase inhibitors, the key may be acting in time. As the disease progresses, it destroys the neurons that have CB_1 receptors, leaving no target on which the cannabinoids can act. The best course of action is prevention, not therapy once "it's too late," de Ceballos says.

Pipe Dreams?

The notion that cannabinoids can help Alzheimer's patients has its critics, among them Lawrence Honig, a neurologist who studies the disease at Columbia University's Sergievsky Center. He maintains that little evidence shows definitively that acetylcholinesterase is involved in beta-amyloid clustering. And looking at Janda's computer models, Honig does not believe that THC works more efficiently than prescription drugs in preventing acetylcholine degradation. He also dismisses the idea that receptors are the key to preventing inflammation or plaque formation.

De Ceballos and Janda are frustrated that their findings are generally unnoticed by the Alzheimer's research field and that their work is stigmatized because the active compound is found in an illegal drug. "Look, we are not advocating that people start smoking dope," Janda asserts. "The only people who take notice of this research are people who are looking for another reason to legalize pot." He believes that prestigious journals have not published his results for this reason.

De Ceballos feels that her research will get the attention it deserves only through communication with the public and physicians so that the message is not misunderstood. Although she is not recommending it, she says that people with a family history of Alzheimer's and who test positive for high-risk genes might consider smoking marijuana at moderate levels over a long period before symptoms arise. "Just like with wine, doctors say 'one glass a day' [for heart health]—not a whole bottle. But it is not something we have data on yet," she points out. In fact, smoking the plant may not even be necessary. De Ceballos notes that another cannabinoid receptor also found in the brain recognizes cannabinoids but does not confer the psychoactive effects. Perhaps one day there will be a pill that targets these receptors instead.

In the meantime, her lab is designing a study of populations from the Netherlands, where marijuana smoking has been decriminalized since 1976. She wants to see if those who indulge in the herb have lower rates of Alzheimer's. If so, the results might finally generate some serious buzz. M

ANDREW KLEIN, a science journalist, formerly researched Alzheimer's disease through the Nathan Kline Institute at the Center for Dementia Research at the Rockland Psychiatric Center in Orangeburg, N.Y.

(Further Reading)

- **A Molecular Link between the Active Component of Marijuana and Alzheimer's Disease Pathology.** L. M. Eubanks, C. J. Rogers, A. E. Beuscher IV, G. F. Koob, A. J. Olson, T. J. Dickerson and K. D. Janda in *Molecular Pharmaceutics,* Vol. 3, No. 6, pages 773–777; November/December 2006.

I Think, Therefore I Err?

Research explores when we can make a vital decision quickly and when we need to proceed more deliberately BY S. ALEXANDER HASLAM

IN GORDIUM in the fourth century B.C., an oxcart was roped to a pole with a complex knot, and it was said that the first person to untie it would become the king of Asia. Unfortunately, the knot proved impossible to untie. Legend has it that when confronted with this problem, rather than deliberating on how to untie the knot, Alexander simply took his sword and cut it in two—then went on to conquer Asia. Ever since, the notion of a "Gordian solution" has referred to the attractiveness of a simple answer to an otherwise intractable problem.

Among researchers in the psychology of decision making, however, such solutions have traditionally held little appeal. In particular, the "conflict model" of decision making proposed by psychologists Irving Janis and Leon Mann in their 1977 book, *Decision Making* (Free Press), argued that a complex decision-making process is essential to guarding individuals and groups from the perils of "groupthink." Decisions made without thoroughly canvassing, surveying, weighing, examining and reexamining relevant information and options would be suboptimal and often disastrous. The Kennedy administration's calamitous decision to invade the Bay of Pigs in 1961 is typically held up as an example of such perils, whereas its successful handling of the Cuban missile crisis in 1962 is cited as an example of the advantages of careful deliberation.

Yet examination of these historical events by Peter Suedfeld, a psychologist at the University of British Columbia, and Roderick Kramer, a psychologist at the Stanford Graduate School of Business, found little difference in the two decision-making processes; both crises required and received complex consideration, and Kennedy just got it right the second time.

Snap Decisions

In general, however, organizational and political science offer little evidence that complex decisions fare better than simpler ones. In fact, a growing body of work suggests that in many situations simple "snap" decisions will be routinely superior to more complex ones—an idea that gained widespread public appeal with Malcolm Gladwell's best-selling book *Blink* (Little, Brown, 2005).

A February 2006 *Science* article by Ap Dijksterhuis of the University of Amsterdam and his colleagues, "On Making the Right Choice: The Deliberation-without-Attention Effect," runs very much in the spirit of Gladwell's influential text. Its core argument is that to be effective, conscious (deliberative) decision making requires cognitive resources. Because increasingly complex decisions place increasing strain on those resources, the quality of our decisions declines as their complexity increases. In short, complex decisions overrun our cognitive powers. On the other hand, unconscious decision making (what the authors refer to as "deliberation without attention," akin to "sleeping on it") requires no cognitive resources, so task complexity does not degrade its effectiveness. The seemingly counterintuitive conclusion is that although conscious thought enhances simple decisions, the opposite holds for more complex decisions. As Alexander showed, it sometimes pays not to think too hard about a complex problem.

Dijksterhuis and his co-workers report four simple but elegant studies supporting this argument. In one, participants assessed the quality of four hypothetical cars by considering either four attributes (a simple task) or 12 attributes (a complex task). Among participants who considered four attributes, those who were allowed to engage in undistracted deliberative thought did better at discriminating between the best and worst cars than those who were distracted and hence unable to deliberate. The opposite pattern emerged when people considered 12 criteria. In this case, conscious deliberation led to inferior discrimination and poor decisions.

JIM FRAZIER Getty Images

In another study Dijksterhuis and his colleagues surveyed shoppers emerging from either the Dutch department store Bijenkorf (which sells "simple" products, such as clothes) or IKEA (which sells more "complex" ones, such as furniture). Compared with those who said they had deliberated long and hard, shoppers who bought with little conscious deliberation felt less happy with their simple purchases at Bijenkorf but happier with the complex purchases at IKEA. Deliberation without attention actually produced better results as the decisions became more complex. Choose your socks carefully—but don't sweat the details about the couch.

Still, it is here, in the realms of society and its governance, that the more problematic implications of deliberation without attention begin to surface. Variables that can be neatly circumscribed in decisions about shopping lose clarity in a world of group dynamics, social interaction, history and politics. Two pertinent questions arise. First, what counts as a complex decision? And second, what counts as a good outcome? Someone shopping for socks or a car may be able to answer these questions straightforwardly. But in the wider world, what constitutes a complex decision or a good outcome is in no sense "given," and a great deal of political energy must be dedicated to defining (and redefining) precisely these things.

Read more about this topic and others at Mind Matters, *Scientific American Mind's* seminar blog on the sciences of mind and brain. Each week top researchers describe their disciplines' most significant new findings. Blog visitors can participate. Join us at www.sciammind.com

The issue here is that when political decision makers err, the fault typically lies less in their psychology or decision-making style than in their politics—and, more particularly, in the relation between their politics and ours.

In the wider world, what constitutes a **complex decision** or a good outcome is in no sense "given."

From there, however, the researchers take a big leap. They write:

> There is no reason to assume that the deliberation-without-attention effect does not generalize to other types of choices—political, managerial or otherwise. In such cases, it should benefit the individual to think consciously about simple matters and to delegate thinking about more complex matters to the unconscious.

This radical inference flies in the face of received political and managerial theory (recall, for instance, Janis and Mann's warnings about groupthink). It doubtless gives succor to would-be Alexanders in politics and management. Indeed, one suspects that many of our political leaders already embrace this wisdom. Who needs the United Nations? Who needs parliamentary process? Who needs democracy? As President George W. Bush put it on June 4, 2003, after having invaded Iraq, "I'm … not very analytical. You know, I don't spend a lot of time thinking about myself, about why I do things."

Yet social psychology suggests that when it comes to decisions affecting groups, the deliberative process itself greatly increases the outcome's viability. New York University psychologist Tom Tyler's studies of criminal justice show that people value not so much the legal system's outcomes as the opportunity to see justice being done. And as social psychology pioneer Kurt Lewin (1890–1947) noted, a "good" decision that nobody respects is actually bad. His classic studies of decision making showed that participating in deliberative processes makes people more likely to abide by the results.

Less Is Less

These are only a few of the reasons why a belief that "less is more" can be dangerous when applied to big decisions. Evidence suggests that for every intuitive manager there is an autocratic tyrant. And for every Alexander who takes the path of nondeliberation to glory, there is a Bush or two who takes it (and us) to somewhere far more problematic.

Like Gladwell's book, the *Science* paper by Dijksterhuis and his collaborators is invaluable in pointing out the limitations of the conventional wisdom that decision quality rises with decision-making complexity. But the sting in the tail is that this work still tempts us to believe that decision quality is simply a question of psychology (in this case, one of matching cognitive load to cognitive resources) rather than also a question of politics, ideology and group membership. Avoiding such social considerations in a quest for general appeal can take us away from enlightenment rather than toward it. Think about it. M

S. ALEXANDER HASLAM is professor of social psychology at the University of Exeter in England and serves on the board of advisers for *Scientific American Mind*.

(Further Reading)

◆ **On Making the Right Choice: The Deliberation-Without-Attention Effect.** Ap Dijksterhuis, Maarten W. Bos, Loran F. Nordgren and Rick B. van Baaren in *Science*, Vol. 311, pages 1005–1007; February 17, 2006.

Paradoxical Perceptions

How does the brain sort out contradictory images?

BY VILAYANUR S. RAMACHANDRAN AND DIANE ROGERS-RAMACHANDRAN

PARADOXES—in which the same information may lead to two contradictory conclusions—give us pleasure and torment at the same time. They are a source of endless fascination and frustration, whether they involve philosophy (consider Russell's paradox, "This statement is false"), science—or perception. The Nobel Prize winner Peter Medawar once said that such puzzles have the same effect on a scientist or philosopher as the smell of burning rubber on an engineer: they create an irresistible urge to find the cause. As neuroscientists who study perception, we feel compelled to study the nature of visual paradoxes.

Let us take the simplest case. If different sources of information are not consistent with one another, what happens? Typically the brain will heed the one that is statistically more reliable and simply ignore the other source. For example, if you view the inside of a hollow mask from a distance, you will see the face as normal—that is, convex—even though your stereovision correctly signals that the mask is actually a hollow, concave face. In this case, your brain's cumulative experience with convex faces overrides and vetoes perception of the unusual occurrence of a hollow face.

Most tantalizing are the situations in which perception contradicts logic, leading to "impossible figures." British painter and printmaker William Hogarth created perhaps the earliest such figure in the 18th century (*a*). A brief view of this image suggests nothing abnormal. Yet closer inspection reveals that it is logically impossible. Another example is the "devil's pitchfork," or Schuster's conundrum (*b*). Such impossible figures raise profound questions about the relation between perception and rationality.

In modern times, interest in such effects was partly revived by Swedish artist Oscar Reutersvärd. Known as the father of impossible figures, he devised numerous geometric paradoxes, including the "endless staircase" and the "impossible triangle." These two were also independently developed by Lionel and Roger Penrose, the famous father-and-son scientists, and *c* shows their version of what is now commonly called the Penrose triangle.

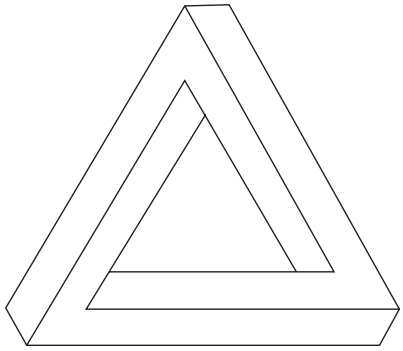
Dutch artist M. C. Escher playfully embedded such figures in his engravings exploring space and geometry. Consider Escher's staircase (*d*): no single part of the staircase is impossible or ambiguous, but the entire ensemble is logically impossible. You could be climbing the staircase upward forever and yet keep going in circles, never reaching the top. It epitomizes the human condition: we perpetually reach for perfection, never quite getting there!

Is this staircase truly a perceptual paradox? That is, is the brain unable to construct a coherent percept (or token of perception) because it has to simultaneously entertain two contradictory perceptions? We think not. Perception, almost by definition, has to be unified and stable at any given instant because

If different sources of information are **not consistent** with one another, what happens?

HISTORICAL PICTURE ARCHIVE *Corbis* (*a*); SCIENTIFIC AMERICAN MIND (*b*)

Are impossible figures genuine paradoxes within the **domain of perception** itself?



c

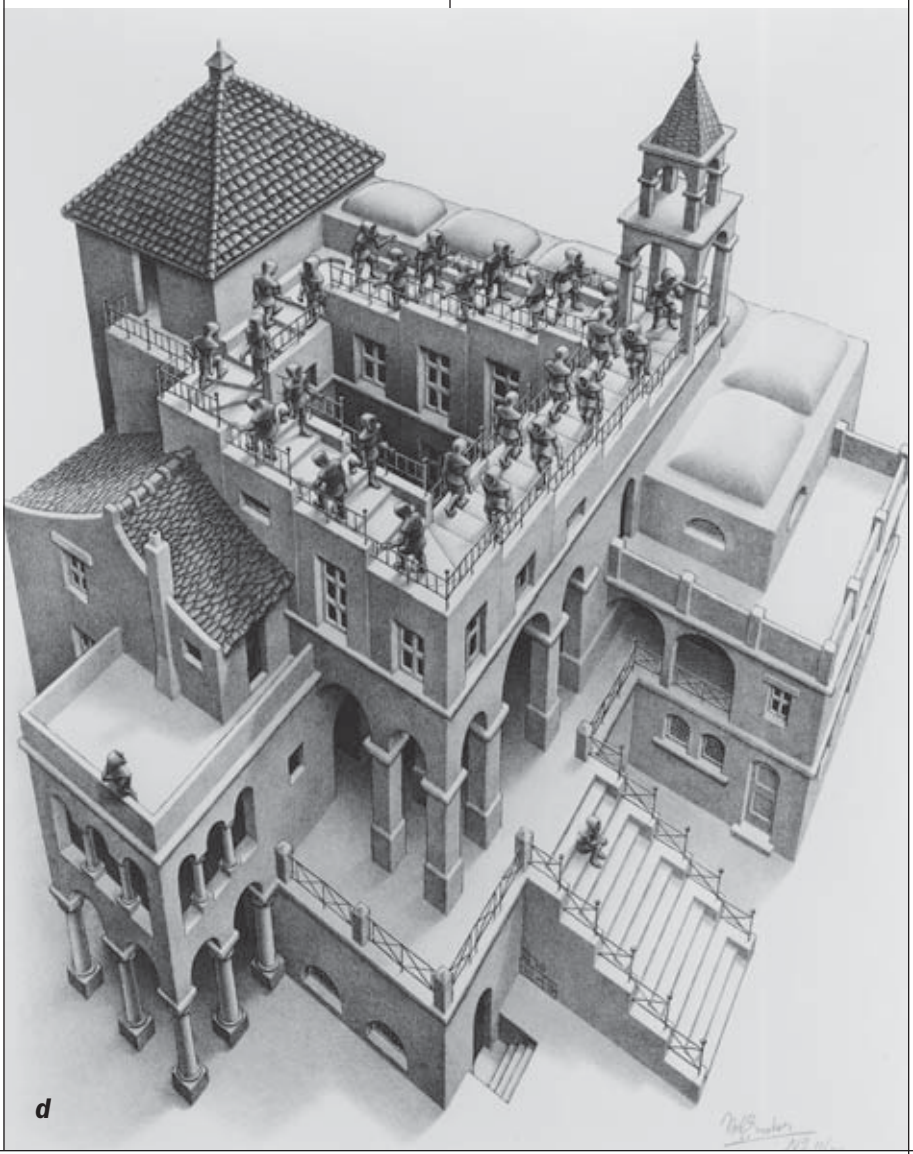
its whole purpose is to lead to an appropriate goal-directed action on our part. Indeed, some philosophers have referred to perception as "conditional readiness to act," which may seem like a bit of an overstatement.

Despite the common view that "we see what we believe," the perceptual mechanisms are really on autopilot as they compute and signal various aspects of the visual environment. You cannot choose to see what you want to see. (If I show you a blue lion, you see it as blue. You cannot say, "I will choose to see it as gold because it ought to be.") On the contrary, the paradox in *d* arises precisely because the perceptual mechanism performs a strictly local computation signaling "ascending stairs," whereas your conceptual/intellectual mechanism deduces that it is impossible logically for such an ascending staircase to form a closed loop. The goal of perception is to compute rapidly the approximate answers that are good enough for immediate survival; you cannot ruminate over whether the lion is near or far. The goal of rational conception—of logic—is to take time to produce a more accurate appraisal.

Genuine or Not?

Are impossible figures (aside from the triangle, to which we will return) genuine paradoxes within the domain of perception itself? One could argue that the perception itself remains, or appears to remain, internally consistent, coherent and stable and that a genuinely paradoxical percept is an oxymoron. The staircase is no more a paradox than our seeing a visual illusion such as the Mueller-Lyer (*e*)—in which two lines of equal length appear to differ—but then measuring the two lines with a ruler and convincing ourselves at an intellectual level that the two lines are of identical length. The clash is between perception and intellect, not a genuine paradox within perception itself. On the other hand, "This statement is false" is a paradox entirely in the conceptual/linguistic realm.

Another compelling perception is the motion aftereffect. If you stare for a minute at stripes moving in one direction and then transfer your gaze to a stationary object, the object appears to move in the opposite direction that the stripes moved. This effect arises because your visual system has motion-detecting neurons signaling different directions, and the stripes constantly moving in one direction "fatigue" the neurons that would normally signal



d

Perception is **virtually instantaneous**, whereas rational conception—logic—takes time.

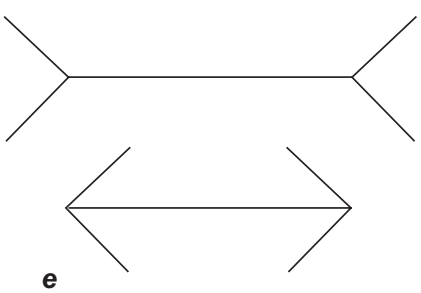
that direction [see "Stability of the Visual World," by Vilayanur S. Ramachandran and Diane Rogers-Ramachandran; Scientific American Mind, February/March 2006]. The result is a "rebound" that makes even stationary objects appear to move in the opposite direction.

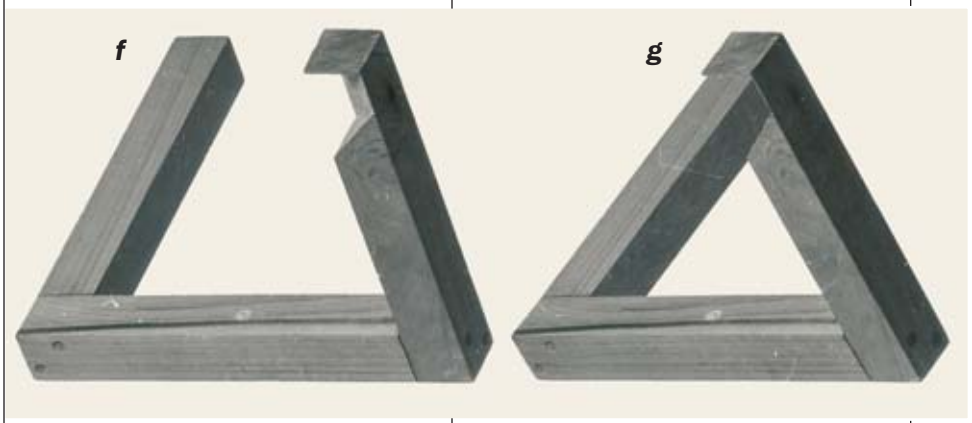
Yet curiously, when you look at the object it seems to be moving in one direction, but it does not seem to get anywhere; it does not progress to a goal. This effect is often touted as a perceptual paradox: How can something appear to move but not change location? But once again, the percept itself is not paradoxical; rather it is signaling with certainty that the object is moving. It is your intellect that deduces it is not moving and infers a paradox.

Consider the much more familiar converse situation. You know (deduce) that the hour hand of your clock is moving, even though it looks stationary. It is not moving fast enough to excite motion-detecting neurons. Yet no one would call a clock hand's movement a paradox.

Perception-Cognition Boundary

There are borderline cases, as exemplified by the devil's pitchfork. In this display, some people can "see" the whole in a single glance. The local and global perceptual cues themselves are perceived as a single gestalt with internal contradictions. That is, one can apprehend the whole in a single glance and appreciate its paradoxical nature without thinking about it. Such displays remind us that despite the modular quasi-autonomous nature of perception and its apparent immunity from the intellect, the boundary between perception and cognition can blur.





The impossible triangle is similar. As shown by Richard L. Gregory, emeritus professor of neuropsychology at the University of Bristol in England, you can construct a complicated 3-D object (*f*) that would produce the image in *g* only when viewed from one particular vantage point. From that specific angle, the object appears to be a triangle confined to a single plane. But your perception rejects such highly improbable events, even when your intellect is convinced of their possibility (after being shown the view at *g*). Thus, even when you understand conceptually the unusual shape of object *f*, you continue to see a closed triangle when viewing *g*, rather than the object (*f*) that actually gives rise to it.

How would one test these notions empirically? With the Escher staircase, one could exploit the fact that perception is virtually instantaneous, whereas cogitation takes time. One could present the display briefly—a short enough time to prevent cognition from kicking in—say, a tenth of a second followed by a masking stimulus (which prevents continued visual processing after removal of the test figure). The prediction would be that the picture should no longer look paradoxical unless the stimulus duration were lengthened adequately. The same could be tried for the devil's pitchfork, which is more likely to be a genuine perceptual paradox. In this case, the mask may not be able to "dissect" it into two distinct (perception or cognition) stages. It may boil down to a matter of scale or complexity.

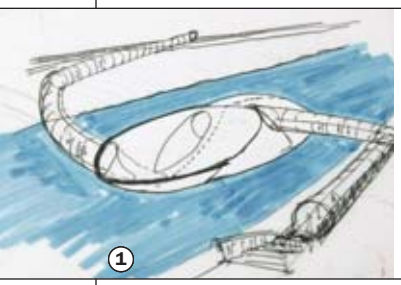
Whatever paradoxes' origins, no one can fail to be intrigued by these enigmatic displays. They perpetually titillate our senses and challenge all our notions of reality and illusion. Human life, it would seem, is delightfully bedeviled by paradox. M

VILAYANUR S. RAMACHANDRAN and DIANE ROGERS-RAMACHANDRAN are at the Center for Brain and Cognition at the University of California, San Diego. They serve on *Scientific American Mind*'s board of advisers.

(Further Reading)

- **A New Ambiguous Figure: A Three-Stick Clovis.** D. H. Schuster in *American Journal of Psychology,* Vol. 77, page 673; 1964.
- **The Intelligent Eye.** Richard L. Gregory. McGraw Hill, 1970.
- More ambiguous figures are available at **im-possible.info/english/art/index.html**

(calendar)



MUSEUMS/EXHIBITIONS

Psychology: It's More Than You Think!
Created by the American Psychological Association, this interactive exhibit explores human behavior, emotions and social interactions, featuring hands-on activities designed to stimulate the imagination. Because its temporary home is in the National Inventors Hall of Fame, the exhibit also includes a historical look at both the psychology of inventors and gadgets invented by psychologists (such as the polygraph).
National Inventors Hall of Fame Museum
Akron, Ohio
Through April 30
330-762-4463
www.invent.org/Exhibit/index.htm

1 Architectural Drawings and Photographs from the L. J. Cella Collection
This collection offers a rare glimpse into the workings of some of the most creative minds in architecture and design, from Frank Gehry to Robert Irwin. Their unique thought processes and moments of inspiration are shown in sketches, drawings, photographs and even napkin doodles.
San Jose Museum of Art
San Jose, Calif.
Through June 3
408-271-6840
www.sjmusart.org

2 Black Box: Takeshi Murata
Takeshi Murata creates short, psychedelic art films full of intense color and hypnotic soundtracks. The show features *Monster Movie* (2005), assembled from a variety of scenes in the 1981 B movie *Caveman.*
Hirshhorn Museum, Smithsonian Institution, Washington, D.C.
May 28–September 9
202-633-1000
http://hirshhorn.si.edu

CONFERENCES

59th Annual Meeting of the American Academy of Neurology
More than 10,000 neurologists and neuroscientists gather once a year to present new research and discuss the cutting edge of brain science. The 2007 program includes a special summit on gene therapy. The association's Web site offers information about the latest breakthroughs and other educational resources for the public.
Boston
April 28–May 5
800-879-1960
http://am.aan.com/

160th Annual Meeting of the American Psychiatric Association
Physicians who specialize in mental health travel from around the world to attend this meeting. The focus for 2007 is "Addressing Patient Needs: Access, Parity and Humane Care."
San Diego
May 19–24
program@psych.org
www.psych.org

MOVIES

Disturbia
In this modernized take on Alfred Hitchcock's *Rear Window,* a wayward teen (Shia LaBeouf) living under house arrest becomes convinced that his neighbor (David Morse) is a serial killer. But are his suspicions just the paranoia of a stir-crazy delinquent?
DreamWorks SKG
Wide release April 13
www.disturbia.com

3 Lucky You
Eric Bana plays a high-stakes poker champ whose shot at winning the World Series of Poker—and the affections of Drew Barrymore's character—is endangered by his complex emotional problems. At the root of his troubled psyche lies his anger toward his father (Robert Duvall), the very poker legend Bana must beat to take the title.
Warner Bros. Pictures
Wide release May 4
http://luckyyoumovie.warnerbros.com

Georgia Rule
Lindsay Lohan in an indie film? Alongside powerhouses Felicity Huffman and Jane Fonda as mother and grandmother, Lohan plays a troubled, rebellious teenager who grudgingly learns compassion and forgiveness while spending a summer under Grandma Georgia's strict control.
Morgan Creek Productions
Wide release May 11
www.georgiarulemovie.net

RADIO/PODCASTS

All in the Mind
This weekly Australian Broadcasting Corporation radio show features in-depth stories on the mind, brain and behavior. Recent topics have included eating disorders, religion versus science, and the psychology of a child soldier. Don't live down under? Listen to the podcast or read the transcript online for free.
ABC Radio National
www.abc.net.au/rn/allinthemind

The Brain Science Podcast
Join Ginger Campbell, an emergency physician, every two weeks as she discusses recent findings in neuroscience and explores how the brain creates our personalities in "the podcast for everyone who has a brain."
http://brainsciencepodcast.com

WEB SITES

4 Classics in the History of Psychology
Christopher D. Green, a psychologist at York University in Toronto, has worked for years to compile a large number of historical writings in this Internet library of psychology. Browse through essays, articles, papers and books written by sages from the ancient Greeks to Freud, Broca, Jung and Darwin. Topics include perception, behaviorism, personality and intelligence.
http://psychclassics.yorku.ca/index.htm

Compiled by Dan Schlenoff and Karen Schrock.
Send items to editors@sciammind.com

VITO ACCONCI, CONCEPT DRAWING #3, *MUR ISLAND,* GRAZ, AUSTRIA, 1999. MARKER AND INK ON PAPER, 18½ X 21 INCHES (1); STILL FROM TAKESHI MURATA'S *MONSTER MOVIE* (2005). COURTESY OF THE ARTIST (2); MERIE WALLACE *SMPSP/WARNER BROS. PICTURES* (3); COURTESY OF HTTP://PSYCHCLASSICS.YORKU.CA/ (4)

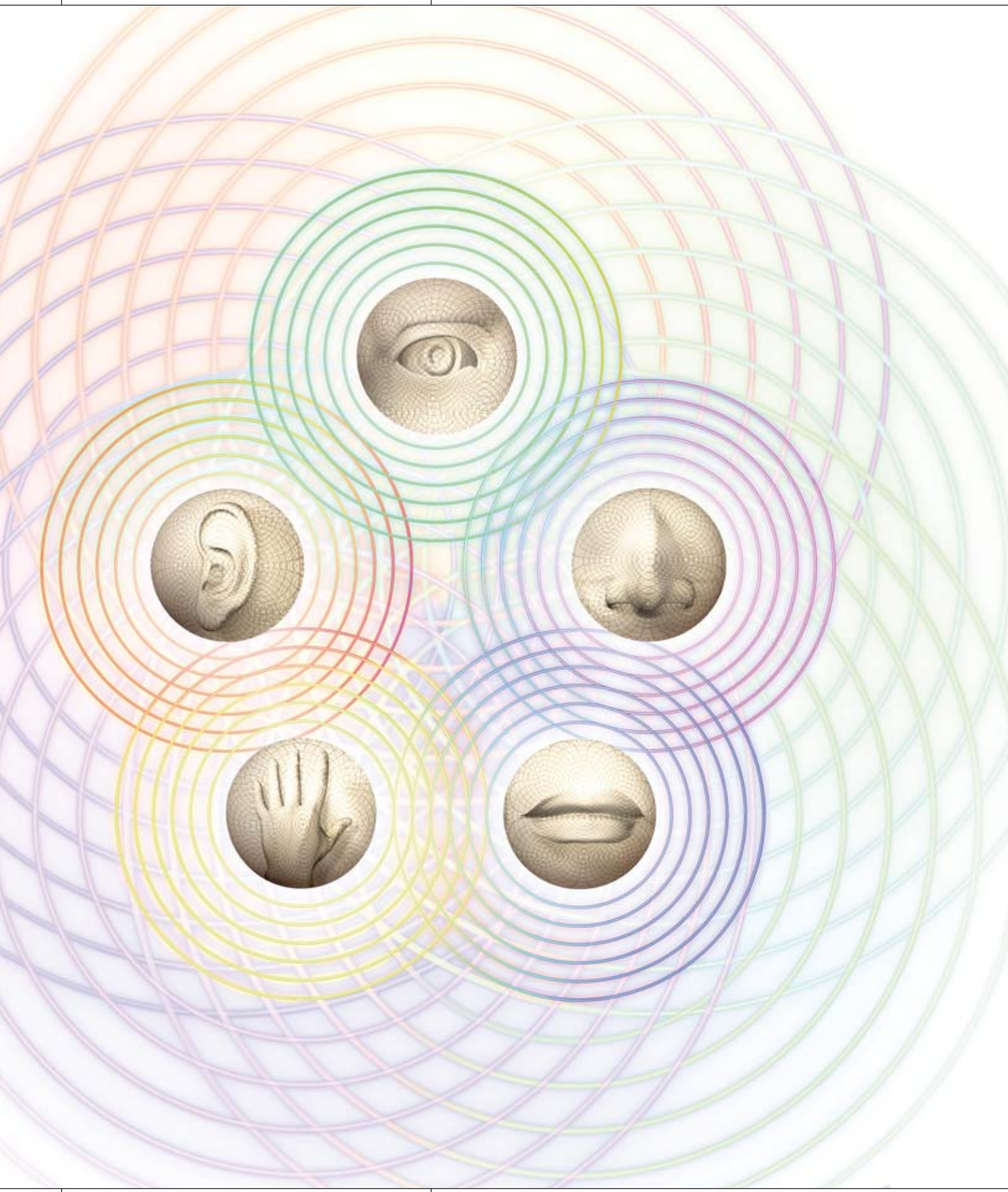
Listening with your Eyes

TO PERCEIVE THE WORLD AS A WHOLE, OUR FIVE SENSES HAVE TO TEAM UP IN THE BRAIN—AND IN SOME CASES, THEY ACTUALLY SEEM TO FUSE WITH ONE ANOTHER BY CHRISTOPH KAYSER

It is Saturday evening at the state fair. To your left, "Rock around the Clock" wafts out of a tent. Behind you, a group of teenagers is carrying on, laughing loudly. Somewhere, an infant is crying. A profusion of neon signs and blinking lights competes for your attention. A roller coaster plummets and makes a hairpin curve. Your senses are already overloaded. But the experience wouldn't be complete without an ice-cream cone in hand and the aroma of cotton candy and honey-roasted almonds in the air.

A scene like this busy fair illustrates just how many signals bear in on us simultaneously from the environment. Yet our brain is able to integrate all the stimuli and make sense of the cacophony of movement and sound. Exactly how this integration happens is not yet understood—which naturally piques the curiosity of neuroscientists.

Illustration by Jean-Francois Podevin



Our different senses do not function as discretely as was previously thought.

The abundance of stimuli typical of a state fair, however, does not lend itself to studying the mind's fusion of the five senses: a process called sensory integration. Researchers tend to be interested in situations in which the brain tricks itself, so to speak, and creates a false picture of its surroundings. In ventriloquism, for example, even though the voice is not coming from the slack-jawed wooden puppet on the ventriloquist's lap, the audience suspends disbelief. By the same token, characters on the silver screen are not actually speaking; their words emanate from loudspeakers distributed around the theater. But when the brain observes lips moving in rhythm with words, it believes the illusion that those lips are the actual source of what is heard. In other words, our auditory and visual impressions work in tandem to create a perception of our surroundings.

But not only do we sometimes misinterpret the source of a sensory impression, we also occasionally perceive it as something entirely different. For example, psychologists Harry McGurk and John MacDonald of the University of Surrey in England discovered an interesting phenomenon in the mid-1970s. They showed a film to volunteers in which a speaker articulated the syllable "ga" but over which they had dubbed the sound "ba." The test subjects reported perceiving neither of these sounds; rather they heard the syllable "da." Visual and auditory information combined to create a third, completely new sound, a process now known as the McGurk effect. Our auditory and tactile senses can create illusory alliances as well. When we rub the palms of our hands together, we can tell how wet they are by sensing not only the amount of wetness we feel but also the sound our skin makes. If we hear a strong rustling noise, our skin feels dry—the fainter or higher-pitched this sound becomes, the wetter the palms of our hands will feel.

Such illusions demonstrate that our brain is constantly combining information from various sensory organs to "draft" a more or less correct image of the environment around us. The question posed for perceptual researchers is: Where and how do our various senses get fused in the brain?

Two basic mechanisms are conceivable. Either the senses function separately and our brain combines their inputs into a coherent whole during the final stages of processing, or else the senses work together from the start, complementing and influencing one another at a very early stage.

Consider the scene of a barking dog in a neighbor's yard. In the first model, each sensory system of the brain first analyzes its particular stimuli by itself and generates its own complete "image" of the environment. For example, our visual apparatus creates the image of a golden retriever barking behind a white picket fence, while our auditory system simultaneously registers both a barking noise and the sound of a passing car. The brain then integrates the sensory impressions to complete the scene: a barking dog in a yard near a street.

In the second model the visual system might first detect a golden brown surface of a given size within a field of green. At the same time, the auditory system picks up a rhythmically repetitive sound from the direction of this surface. The visual system then registers that the surface changes when the auditory system perceives the sound. The various senses complement one another within a few fractions of a second until the overall impression of a barking golden retriever emerges. In this mechanism, sensory integration occurs at a very early phase of processing.

These two scenarios are the extreme ends of a spectrum of possible mechanisms for sensory integration. An infinite number of intermediate stages between these two variants is conceivable. Presum-

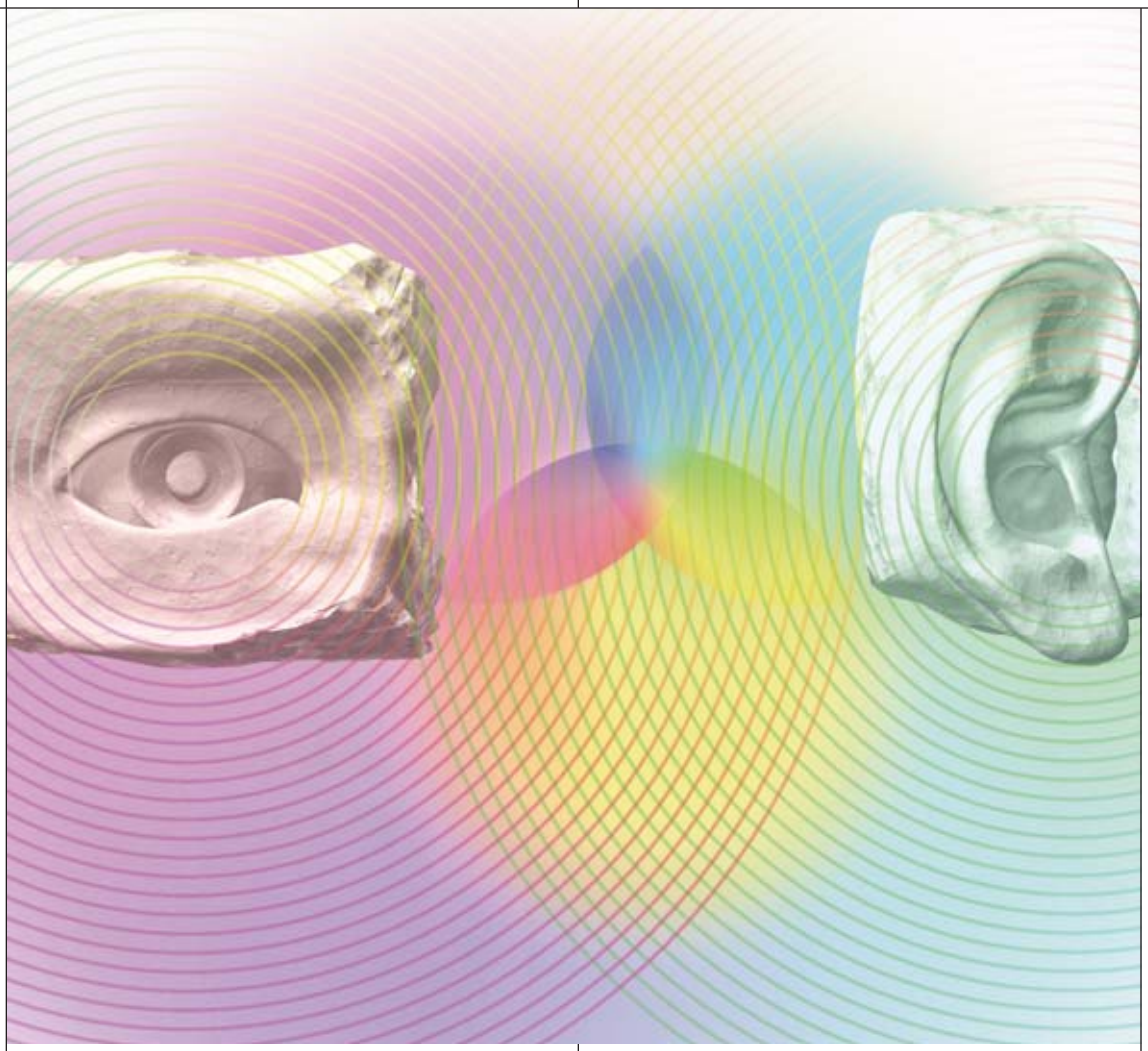
FAST FACTS

Meaningful Fusion

1» The brain receives information from the sensory organs via different channels. Only by combining this information—sensory integration—can we gain an overall unitary image of our surroundings.

2» As new research shows, this integration occurs early on during the processing of neuronal stimuli. Even brain centers that specialize in a given sense use information from other sensory channels.

3» Here is a good example of this "sensory crossover": certain regions of a superordinate auditory region—the secondary auditory cortex—also process visual and tactile stimuli. In other words, our eyes and fingers help us listen.



Far from being specialized and independent, our five senses work together to enhance our perception of the world around us.

ably the path that the brain actually takes is somewhere in the middle. The question is, Where?

Images of Integration

Psychologists first began investigating interactions among the senses in the 1950s by examining how different sensory combinations affect our perception of the world around us. They quantified illusions such as the McGurk effect, mentioned above, and the ventriloquist effect, first described in 1966 by Ian P. Howard and W. B. Templeton, who were researchers at York University in Toronto. Even today psychological studies continue to explore perceptual illusions to find out how our brain combines different aspects of sensory information and how this improves our performance in tasks that rely on multisensory information.

Around the 1970s, as psychologists were investigating sensory integration from a perception standpoint, scientists coming from more classical biological fields such as neurophysiology started to investigate the neuronal basis of how the brain combines sensory information. But whereas many of these researchers investigated neurons related to specific senses, such as those in the visual or auditory pathways, only a small minority studied multisensory properties. Only recently, helped in part by advances in brain-imaging techniques, have people begun to realize that our different senses do not function as discretely as was previously thought.

Technology such as functional magnetic resonance imaging (fMRI) makes use of the fact that when an area of the brain works particularly hard, it needs more oxygen than adjacent regions and is therefore more heavily perfused with blood. Oxygen-rich hemoglobin molecules behave differently in a strong magnetic field from those that contain no oxygen, so fMRI scanners

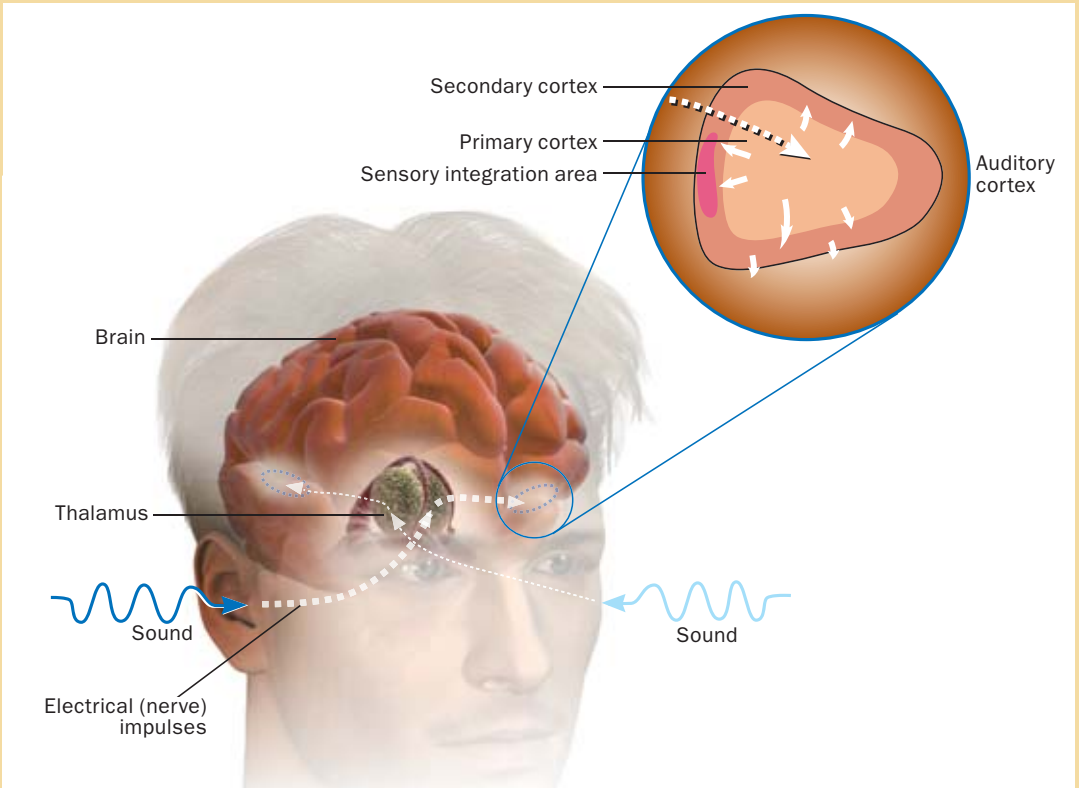
(The Author)

CHRISTOPH KAYSER is a mathematician and has a doctorate in natural sciences. He is currently researching the integration of sensory information at the Max Planck Institute for Biological Cybernetics in Tuebingen.

JEAN-FRANCOIS PODEVIN

Where the Senses Meld

The sensory impulses generated in the inner ear first reach the primary auditory cortex via the thalamus and then enter the secondary auditory cortex. This region is where the signals merge with other sensory information.



can detect blood flow and therefore produce images of the working brain.

Now consider again the neighbor's barking dog: fMRI scanning should be able to detect the difference between the two models of sensory integration. If the first model is correct and sensory information is analyzed separately by the various systems and then combined at the end, many different regions of the brain should be engaged, and each should exclusively process a single sense. On the other hand, if the information is combined early, only a few highly specialized regions should suffice.

Over the past several years, a series of imaging studies has disclosed a complex network of brain regions that are activated most strongly when various sensory data fuse. It has long been known that so-called associational regions in the parietal and frontal lobes of the cerebral cortex process information streaming in through various sensory channels. Yet regions that up to now have been thought to be responsible for only one sense have recently been demonstrated to have a broader spectrum of talents. As Jon Driver of University College London described in 2000, activity in the visual cortex of test subjects who have just seen a short flash of light in the vicinity of their right or left hand increases when the fingers of that hand also perceive tactile stimuli. This increased brain activity only occurs, however, when the visual and tactile stimuli occur simultaneously *and* on the same side of the body.

Psychologists have known about this "multimodal reinforcement" for quite some time. For example, people have more trouble seeing a flickering point of light as its intensity decreases. Yet if we hear a short burst of sound at the same time as the flickering, we will perceive even the weakest glimmer of light. But this effect works only when the light and the sound are precisely synchronized.

The perception of language is particularly interesting. As the McGurk effect demonstrates, the spoken word is not only conveyed acoustically. Lip

GEHIRN & GEIST/SIGANIM

Even the soundless image of a person speaking is sufficient to stimulate the auditory cortex.

movements communicate important information as well. In 2001 psychologist Gemma Calvert, now at the University of Bath in England, observed that speech perception increases the activity of both the auditory and the visual system when acoustic and visual stimuli are perceived simultaneously. In other words, the image of moving lips affects the processing of acoustic signals early on. This synergy between hearing and seeing occurs in regions of the brain that had previously been viewed as separate sensory regions.

Even the soundless image of a person speaking is sufficient to stimulate the auditory cortex measurably, including when the speaker is talking gibberish. On the other hand, making faces leaves the auditory cortex cold. This phenomenon makes it clear that the auditory cortex reacts specifically to the visual image of speech, and the sensory integration of acoustic and visual stimuli facilitates speech processing.

Fusion in the Brain

Accordingly, the second model, which presumes early sensory fusion, appears to be much more accurate. My team's research at the Max Planck Institute for Biological Cybernetics in Tuebingen also points in this direction. In 2005 we performed high-resolution magnetic resonance measurements on various regions of the auditory cortex of rhesus monkeys (*Macaca mulatta*). The auditory cortex comprises various subunits [*see box on opposite page*]. The primary auditory cortex receives the electrical impulses produced by sound waves in the inner ear, via a mediator in the thalamus. Then those impulses travel to the higher auditory regions, which surround the primary auditory cortex like a belt only a few millimeters thick.

We measured the increased activity in the auditory cortex while we played rustling noises to the animals through a headset and stimulated their palms or the soles of their feet with a brush. When we did both simultaneously, the posterior end of the secondary auditory cortex in particular was stimulated. Earlier this year we saw similar results in a new study in which we used visual instead of tactile stimulation. Again we found that only the posterior half of the auditory cortex was stimulated. This is where sensory integration appears to occur.

We do not yet know why sensory information fuses in these particular brain regions. But it appears that the posterior part of the auditory cortex is specialized for registering spatial information—that is, recognizing the directionality of a sound. Perhaps the sensory fusion that occurs here contributes to the relating of various sensory impressions to a particular source in space.

In January a groundbreaking study by neuroscientist Charles Schroeder and his colleagues at the Nathan S. Kline Institute for Psychiatric Research in Orangeburg, N.Y., revealed a mechanism by which nonauditory stimulation enhances activity in the auditory cortex. The researchers found that although a tactile stimulus alone will not cause auditory neurons to fire, it will manipulate the underlying oscillatory pattern in the neurons so that they have maximum firing potential. This way, if the auditory cortex simultaneously receives auditory and tactile stimuli, its neurons will fire more strongly than they would if auditory stimuli were received alone. This new insight helps to explain how receiving information from two different sensory organs causes both processing centers to activate more strongly, and it might point to the neuronal basis of sensory integration.

Although we are still working toward a complete understanding of how the brain processes sensory information, one thing seems certain: sensory integration occurs in high-level regions, and it occurs early in the process, though not as early as one might assume on theoretical grounds. The first model, which assumes separate processing of sensory impressions, is simply false. The second model, which assumes that the senses are fused at the earliest possible moment, is overstated but fits reality better. Clearly, many regions of the brain are engaged in combining information from different senses, and a much smaller part of the brain than previously thought is dedicated exclusively to each individual sense. M

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Through a Glass, Darkly

A distorted body image is symptomatic of nearly all eating disorders. Correcting this mental reflection can help sufferers recover

By Christian Eggers and Verena Liebers

They all look the same in front of the mirror—attractive and slim—but one after another, they get up in swimsuits and bemoan their physical faults: fat thighs, shapeless silhouettes, flat chests. These young women are participating in group sessions focused on body image, co-sponsored by the universities of Bochum and Mainz in Germany. Senior therapist Silja Vocks knows she will have a hard time getting through to these girls, who all suffer from eating disorders, but it is her job to help them learn to like themselves again.

GETTY IMAGES

MAX OPPENHEIM Getty Images

In the U.S., recorded cases of eating disorders have doubled since the 1960s.

Eating disorders are complex psychiatric conditions, instigated by a number of factors both inborn and circumstantial. For most patients, however, significant mental pain stems from having a faulty body image, a term psychologists use to describe an individual's internal picture of his or her exterior form. In truth, this image more accurately reflects self-esteem than physical appearance. It is based not so much on fact as on emotion, and the opinions of family and peers, as well as cultural ideals, can dramatically alter its dimensions.

Most people have body images that roughly match their shape. For those with eating disorders, though, this mental picture becomes warped like a reflection in a fun-house mirror: severely distorted and often grossly obese. Ideally, treatment plans must be multifaceted, including nutritional, medical, psychiatric and psychotherapeutic interventions. But as programs such as Vocks's show, tackling body image head-on can offer some patients a first step toward escaping the vicious cycle of an eating disorder.

Starve, Binge, Purge

Finding new and more effective ways to treat eating disorders is vital. Their incidence continues to rise in the developed world; in the U.S. alone, recorded cases have doubled since the 1960s. Although the true prevalence of these disorders is hard to establish, an estimated 0.5 to 3.7 percent of women develop anorexia nervosa and some 1.1 to 4.2 percent experience bulimia nervosa in their lifetime, according to the National Institute of Mental Health. Within any given six-month period, another 2 to 5 percent of

Americans succumb to a binge-eating disorder.

Of the three, anorexia nervosa is most deadly. Sufferers starve themselves, exercise excessively and still think they are too fat, even when their bones jut out from their skin. With each pound shed, they become increasingly out of touch with their bodies, only poorly registering hunger, cold, heat and even pain. Hormonal disturbances can set in: women often stop menstruating, and men experience impotence. Other physical consequences include low blood pressure, a variety of skin problems and fluid retention.

Even as their bodies begin to collapse, many anorexics remain obsessed with control and performance. They are often proud of their ascetic lifestyle and feel they gain strength from their ability to do without. Such stringent self-discipline can have fatal consequences. Statistically, only 30 percent of anorexic women make a full recovery. About 35 percent regain some weight but maintain a distorted body image. Another 25 percent are chronically anorexic, and 5.6 percent die from starvation or suicide over the course of a decade.

Whereas anorexia nervosa typically develops around puberty, bulimia nervosa more normally appears between the ages of 18 and 35. These patients fluctuate between two extremes—starvation and binging. During binge phases, bulimics stuff themselves with calorie-rich food. Afterward, however, they feel shame and either regurgitate what they have just eaten or abuse diuretics or laxatives as compensation. This purging is extremely damaging: stomach acid in their vomit erodes their teeth and harms cells in the esophagus, which can lead to cancer. Electrolyte imbalances—a result of dehydration and potassium and sodium depletion—can cause organ damage and cardiovascular problems, including heart attacks.

Despite these life-threatening complications, bulimia nervosa often goes unnoticed, even by medical professionals. Victims usually sustain a normal weight and keep their binging and purging practices well hidden. Once exposed, bulimics who seek treatment have a 50 percent chance of making a full recovery. As for the half who remain unwell, they may adopt vomiting as a permanent habit, or they may fall into a kind of gray zone between recovery and illness. Some of these patients slide into binge eating, continuing to overeat while no longer purging.

For all their differences, anorexia, bulimia and binge eating exist along a continuum and usually emerge after a period of dieting. Those who succumb typically start out hoping to lose a few pounds but end up slashing fats, sugars and carbohydrates until all thoughts revolve around a single question: What am I permitted to eat? Almost half of all women have dieted at some point. But frequent and extreme dieting quickly scrambles the body's hunger-satiety system, paving the way to problem behaviors and faulty perceptions.

FERNANDA CALFAT *Getty Images*

After the deaths of two South American models last year from anorexia nervosa, Madrid and Milan banned ultraskinny models from Fashion Week runways. Still, models strive toward size zero, equivalent to a 22-inch waist, the average for an eight-year-old girl.

Mirror, Mirror

What lies behind a distorted body image? To answer this question, Vocks's team took photographs of 56 people suffering from eating disorders and 209 healthy subjects used as controls. The scientists then asked the test subjects to adjust their images on a computer screen until they "recognized" themselves. Additionally, they asked both groups to give their virtual "me" the figure that they wished they had. Whereas all the respondents had similar notions of an "ideal" figure, the bulimics and anorexics all significantly overestimated their real body mass. In contrast, the subjects who were not suffering from

(The Authors)

CHRISTIAN EGGERS is a pediatric psychiatrist and psychotherapist. He has been the director of the Pediatric and Child Psychiatry Clinic in Essen, Germany, for 25 years. **VERENA LIEBERS** has a Ph.D. in biology. She is an artist, journalist and scientist who lives in Bochum, Germany.

A faulty body image—rather than an exaggerated ideal—is crucial to the development of eating disorders.

eating disorders believed that they were slimmer than they actually were.

Barbara Mangweth, a psychologist at the Innsbruck Medical University in Austria, reached similar conclusions in a study of men suffering from eating disorders conducted in 2004. In collaboration with researchers at the Biological Laboratory of Psychiatry at McLean Hospital in Belmont, Mass., Mangweth compared 27 anorexic and bulimic men with 21 male mountain climbers and 21 male controls. The subjects held similar ideas about the ideal male figure but proffered dramatically different assessments of their own bodies. Unlike the climbers and the controls, the bulimics and anorexics all believed that they had about twice as much body fat as they actually had. Mangweth concluded that a faulty body image—rather than an exaggerated notion of what is ideal—is crucial to the development of eating disorders.

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We still do not have an adequate understanding of why some people are subject to such distortions. Vocks and her colleagues suspect the problem involves information processing. According to their theory, the sensory organs of people with eating disorders correctly register their form, but negative thoughts filter the input. For example, memories of being teased about their looks as a child or teen may override how some bulimics and anorexics would otherwise see themselves. Because these individuals lack the emotional support to hold up a more flattering view, insecurity flourishes in them.

Self-Reflection

Clearly, insecurity helps to warp body image. Our view of ourselves often comes from how others see us or how we think they see us. If this reflection is not sufficiently positive, self-image will suffer, sometimes from the very start of childhood. Optimally, parental nurturing leads to a sound relationship balanced between security and independence. Yet studies have confirmed that some 30 percent of all children lack such an attachment relationship. Without feeling safe and accepted, these children are at risk of falling into an addictive cycle involving food or other substances.

Other family dynamics contribute to poor self-image. Although eating disorders occur in all kinds of families, those affected often share certain traits. They are typically well situated and well educated and, to the outside world, appear to function harmoniously. Frequently, however, the children feel tremendous pressure to excel, the parents set high standards, and negative emotions such as anger or jealousy are suppressed. In keeping with these high standards, people with eating disorders strive to be model students or, as adults, to lead perfect lives. Even so, they usually feel that they never measure up.

Apart from a dearth of positive feedback, some individuals develop eating disorders in response to specific childhood traumas. According to the findings of Stephen Wonderlich's group at the Eating Disorders Institute in Fargo, N.D., sexual abuse in particular may increase the odds. Similarly, children whose parents are divorced or alcoholic are clearly at risk. Several teenagers seen at the Pediatric and Child Psychiatry Clinic in Essen, Germany, where one of us (Eggers) is

Beauty Is Truth

Dove's Campaign for Real Beauty, featuring "real women with real curves," aims to help women who are not model-thin embrace their unique beauty. In 2004 Dove commissioned a global study from Nancy Etcoff of Harvard University, Susie Orbach of the London School of Economics, and Jennifer Scott and Heidi D'Agostino of StrategyOne, an applied research firm based in New York City. After interviewing some 3,200 women in 10 countries, the authors found that only 2 percent considered themselves beautiful and that almost half believed they were too fat.

DOVE

director, reported that they felt overwhelmed when their parents divorced, unable to mediate or remain loyal to both sides. Self-hatred can easily arise from such perceived inadequacy—with terrible long-term consequences.

Certainly eating disorders are not exclusively the result of personal problems, but negative feedback from or neglect by family and friends can, at least in part, predispose an individual to anorexia, bulimia or binge eating. In these instances, many parents do not know how to help and feel guilty that they are unable to guide their child. As a result, family therapy can be an important component of an overall strategy in which problems are worked out together. Frequently, the eating disorder is merely the last link in a chain of unhappy events.

Unrealistic Ideals

The standards of beauty promoted by Hollywood films and the fashion industry today only magnify the problems behind most eating disorders. Until the end of the 19th century, curvaceous women were considered just as beautiful as their less voluptuous sisters. But aesthetics changed dramatically during the century that followed. Studies show that most people now prefer the look of bodies that weigh several percentage points below normal.

It is difficult to measure the direct effect that glossy magazines and other media images have on dieting behaviors, but Fiji offers an interesting case study. Anne E. Becker, director of the Adult Eating and Weight Disorders Program at Massachusetts General Hospital, documented eating habits in the Pacific nation throughout the 1990s. In 1995—almost immediately after the introduction of television on the island—she found that only 3 percent of schoolgirls, who were on average 17 years old, reported that they had vomited to control their weight. By 1998, though, that number had surged to 15 percent. And 74 percent of the girls described feeling "too big or fat" at least sometimes, even though Fijians traditionally associate robust body shapes with higher social rank.

For those in Vocks's program, finding the courage to bare their perceived faults in front of a group does often pay off. The 90-minute sessions are no substitute for long-term treatment, but Vocks's patients frequently change their eating habits for the better and often manage to raise their own battered sense of self-worth. Perhaps most important, many learn that the body they have long hated is beautiful in another's eye. M

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Addicted to FOOD?

What drives people, against their better judgment, to eat more food than they need? Scientists look to the brain for answers

By Oliver Grimm

It's been a long day, and you are still at the office. With your blood sugar plummeting, your brain starts to obsess: Where can I get some food? You gather your money and dash across the street to the fast-food place. But as you bite into the greasy burger, your conscience suddenly kicks in: What am I doing?

It is a common scenario for many of us. Hunger is a potent, if only temporary, condition that can overpower our very best nutritional intentions. In its absence, the brain's cerebrum—governing conscious behavior—helps us make healthy, informed decisions about what we eat. But when our stomachs begin to growl, too often they drown out any good advice coming from our brains. Unfortunately, the short-sighted decisions we make with our stomachs are having an increasingly negative effect on our health.

Research into overeating and obesity has accelerated in recent years, and with good reason: excess weight is the most important risk factor for cardiovascular disease and diabetes. According to a study by researchers at the Centers for Disease Control and Prevention and the National Cancer Institute, obesity was associated with about 112,000 deaths in 2000 in the U.S. In addition, a 2002 study in the journal *Health Affairs* estimated annual medical spending on overweight and obese patients to be as much as $92.6

CHARLES THATCHER Getty Images

billion—or 9.1 percent of the country's health expenditures. Physicians define obesity as having a body mass index, or BMI, higher than 30. Anyone with a BMI above 25 is overweight. (You can calculate your own BMI at www.nhlbisupport.com/bmi) By these measures, about one third of American adults are overweight, and nearly another third are obese, according to the National Health and Nutrition Examination Survey, conducted between 2003 and 2004.

"Stop" Hormones

In their quest for causes, scientists have long concentrated on metabolic hormones. In 1994 Jeffrey M. Friedman of the Rockefeller University discovered that adipose tissue, or fat, possesses a feedback mechanism by which it can block additional eating. Indeed, fat cells secrete a protein that passes through the blood to the hypothalamus in the brain, where it suppresses feelings of hunger. Friedman dubbed the substance leptin, from the Greek *leptos,* meaning "thin."

When researchers genetically engineered mice in which leptin could not function, the animals rapidly became obese. The results led some to speculate that obesity might stem from little more than a faulty feedback mechanism—and not human behavior. On closer examination, however, this interpretation turned out to be too

(The Author)

OLIVER GRIMM is a psychiatrist at the Central Institute for Mental Health in Mannheim, Germany.

Hunger is a potent, if temporary, physical condition that can overpower our very best nutritional intentions. When our stomach begins to growl, too often it drowns out any good advice coming from our brain.

one-sided. Leptin, we now know, also plays an important role in addictive behavior. Heroin-addicted lab animals suffer even more during withdrawal if they are kept hungry. Perhaps this satiety hormone suppresses cravings not only for food but for certain drugs as well.

Is Food a Drug?

Anyone who has ever dieted knows how hard it is to kick old habits. Should we view overweight people as addicts of a sort? The comparison seems far-fetched at first glance. After all, a person who eats too much does not develop a food tolerance, and overweight dieters certainly do not suffer the terrible physical symptoms of withdrawal. But obese people do show some hallmarks of dependency, among them a strong drive to eat and a loss of control to the point of neglecting other needs.

As it turns out, drug addiction and binge eating are not dissimilar in neurobiological terms. Bundles of nerve fibers that run from the midbrain to a structure called the nucleus accumbens secrete unusually large amounts of the neurotransmitter dopamine whenever we experience something surprising or pleasant. If a hungry lion, for example, spots a nice piece of meat, its nucleus accumbens is flooded with dopamine. Likewise, cocaine and amphetamines cause dopamine levels in the nucleus accumbens to rise at least 10-fold, delivering a rush of pleasure.

This reward system further controls the hypothalamus, which, among other things, regulates eating behavior. Mice that have been genetically modified so that they no longer produce dopamine reveal just how important this connection is. The animals lose all desire to consume anything and simply starve. Once provided with dopamine, however, their eating behavior returns to normal.

In 2001 Gene-Jack Wang of Brookhaven National Laboratory and Nora Volkow of the National Institute on Drug Abuse confirmed the important role dopamine plays in eating. Using positron-emission tomography (PET), they measured the quantity of dopamine receptors in the striatum of overweight volunteers and found that this amount correlated closely to BMI. The higher the subject's BMI, the fewer dopamine receptors he or she had. The researchers concluded that, like drug addicts, extremely overweight individuals suffer from a dopamine shortage, causing them to constantly seek new rewards in the

FAST FACTS

Addiction and Obesity

1» **Obesity is associated with about 112,000 deaths a year in the U.S. By some estimates, annual medical spending on overweight and obese patients constitutes 9.1 percent of U.S. health expenditures.**

2» **Drug addiction and binge eating are not dissimilar in neurobiological terms. Recent research makes it clear that the brain's reward systems play a key role in the control of eating behaviors.**

3» **Neurobiology is showing why it can be so hard for overweight people to lose weight: for all their differences, drug addiction and obesity may be two sides of the same coin.**

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The brain processes stimuli related to eating in much the same way it responds to addictive substances.

form of food. But their brain then compensates for the excess dopamine that follows by reducing its number of dopamine receptors—a mechanism known to occur among cocaine addicts.

In a 1930s experiment that targeted a different brain system, apes became eating machines. German neuroscientist Heinrich Kluever and his American colleague, Paul C. Bucy, destroyed the animals' amygdala, a brain region involved in arousal and emotional responses. The finding suggested that it plays a role in satiety. Kevin LaBar of Duke University picked up this thread of research in 2001, taking magnetic resonance imaging (MRI) scans of the amygdala in nine human subjects as they looked at pictures of either food or nonfood items, such as cars or tools. The test subjects were healthy but hungry, having fasted for eight hours before the experiment. Once tested, they were given a meal of their choice and then put back inside the scanner.

In this way, LaBar was able to compare the brain activity of a hungry person to that of a sated one. He found that a hungry subject's amygdala became active the instant he or she saw anything edible. Once the person had eaten, though, this brain region no longer responded. Clinton Kilts and his colleagues at Emory University carried out similar experiments on cocaine addicts at roughly the same time. As PET scans revealed, the amygdala also reacted immediately when these subjects were shown images sure to excite them, including thin lines of white powder. Apparently the amygdala acts as a kind of alarm bell. Anytime it detects something important to the organism's survival—be it a big snake or a tempting sandwich—it rings.

Overeating as Habit

Yet another brain region, the orbitofrontal cortex (OFC), is involved in human addiction. The OFC, which lies in the frontal lobes just above the orbits of the eyes, seems to function as a control center monitoring our behavior. People with an OFC that has been damaged by accident or disease, for example, are frequently unable to control themselves. They act impulsively and demonstrate some degree of addictive behavior. And the OFC is significantly less active in drug addicts than it is in healthy people.

In 2001 Dana M. Small, now at Yale University, demonstrated that the OFC also processes food-related pleasures and aversions. She took PET scans of nine subjects while they let their favorite chocolate melt on their tongues. Brain activity increased in areas associated with sensory inputs but even more so in the OFC. Next the researchers asked their subjects to eat chocolate until their enjoyment turned to disgust. At that point, the central part of the OFC suddenly switched off, and activity increased instead in the adjacent region, the lateral OFC.

All these experiments support a single idea: the brain processes stimuli related to eating in very much the same way it responds to other addictive stimuli. So although some obese patients can trace their problem directly to hormonal imbalances, behavioral control plays a considerable role.

We hope that as we gain a better understanding of how the brain handles feelings of hunger and satiety, we will be able to develop more effective therapies for overeating and obesity. Medications developed to treat drug addiction already show some promise. For instance, patients who take naltrexone, an opiate antagonist that blocks the pleasure associated with opiate narcotics, typically stop gaining weight. Another drug called rimonabant, which blocks a receptor of the endogenous cannabinoid system, helps some patients lose weight, though often not much.

Of course, counseling, exercise and healthy eating habits give better results than anything else. But neurobiology now shows just why that route can be so hard: for all their differences, drug addiction and obesity seem to be two sides of the same coin. M

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Freeing a (Locked-In) Mind

Vegetative patients may soon be able to communicate with the outside world

By Karen Schrock

The patient opens her eyes, but they are unfocused. She is awake yet apparently unaware of anything going on in the hospital room around her. After the accident, she lies in her bed, unresponsive, day after day. What is she thinking?

ANGELA WYANT *Getty Images*

Soon we may be able to communicate with such "locked-in" minds—trapped in bodies that no longer respond to their mental control. In a blitz of publicity last fall, a team of British researchers announced they had imaged the brain of one of their "vegetative" patients and discovered that she was in fact conscious and aware. Now that same team has developed a way to ask yes-or-no questions of such patients. The idea is radical: we might soon be able to reach a number of people, including 250,000 Americans, who suffer from consciousness disorders—patients who, until now, had been considered beyond treatment.

> Patients can literally communicate without having to say or do anything.

"We are now able to detect when somebody is consciously aware, when existing clinical methods have been unable to provide that information," says Adrian Owen of the University of Cambridge, leader of the team of researchers who imaged the woman's brain as she responded to doctors' requests that she imagine such activities as playing tennis. Because of recent advances in imaging technology, patients "can literally communicate without having to say or do anything," Owen says.

A Shift in Thinking

"People have felt until now that this patient group isn't worth investing in. The attitude has been, 'There's nothing that can be done,'" Owen adds. Decades ago the medical community provided nothing more than palliative care for patients with disorders of consciousness who could not wake up or who were not aware of their surroundings. These brain-damaged patients were kept clean and comfortable until they died.

Once in a while, however, one of these patients would recover unexpectedly. When someone woke up out of a decade-long coma, the revival would be considered a miracle or, at the very least, a medical mystery. There seemed to be no way to determine if a patient with brain damage would come to or not. The only thing to do was wait and see.

But beginning in the 1970s, the scientific field of neurorehabilitation came into existence. Rehab centers, where patients could receive treatment from specialists, sprang up around the country. Doctors began to consider each brain injury individually, tailoring unique drug regimens and physical therapies in an attempt to improve each patient's condition. That was the best they could do, however: traditional magnetic resonance imaging (MRI)—used since the 1980s to map the structure of the brain or other areas inside the body—made it possible for doctors to see physical damage to the brain but did not allow them to examine its activity.

Then, in the 1990s, with the advent of functional MRI (fMRI) scans, it became possible to study activity in living brains. Functional MRI allows researchers to see which areas of the brain are most active during thought processes, which is how Owen and his colleagues determined that their vegetative patient was indeed aware and responding to their commands. Slowly, neuroscientists' understanding of brain damage began to move forward. Brain-damaged patients were no longer automatically considered lost causes but rather victims of a condition for which there might someday be a cure.

"Functional imaging is really the first imaging technique that has allowed us to look at the inner cognitive workings of patients who have disorders of consciousness," says Joy Hirsch, a neuroscientist at Columbia University. In 1992 scientists discovered they could use an MRI scanner to map changes in blood flow to different areas of the brain, signaling which parts of the brain were working during any given thought process or sensory stimulation. In the subsequent decade, researchers determined the difference in the fMRI patterns of willful thought and passive response to stimuli, a crucial distinction when examining the brain of a patient whose state of consciousness is unknown. Now fMRI technol-

FAST FACTS

Trapped No Longer

1» Some brain-damaged patients may be conscious of their surroundings but unable to control their body to communicate that awareness.

2» Now researchers are using fMRI scanning to "talk" directly to these patients' brains, a breakthrough that could lead to new treatments.

ogy has improved such that researchers can give patients commands and analyze their responses within a minute rather than a month. The result: we are on the verge of communicating with patients who only a few years ago would have been considered brain-dead.

Of course, not all patients can improve: some simply do not have enough brain structure left. "We've seen several recent cases that tell us that in some of these patients there is some chance of recovery," Owen explains. "But certainly not in all patients." This was the case with Terri Schiavo, a permanently vegetative Florida woman who became the center of a political debate in 2005 when her parents challenged her husband's decision to remove her feeding tube and let her die. A computed tomographic (CT) scan showed that much of her brain had atrophied, and doctors were unanimous in their opinion that she would not recover.

Determining a brain-damaged patient's prognosis is not always so cut and dried. The brain is a fragile organ; it can be damaged in many different ways, most of which are poorly understood by science. Whereas a number of patients might regain partial or complete use of their faculties, others truly are permanently injured with no hope of recovery. In a few cases, the victims might be aware of their surroundings but unable to respond. Still others are unconscious *and* unaware. The difficulty lies in determining which patients are which.

The first step is getting a general understanding of the patient's state of mind. Clinicians divide disorders of consciousness into three categories: coma, in which a patient is neither awake nor responsive; vegetative, in which a patient is awake but unresponsive; and minimally conscious, in which a patient is awake and responds to stimuli but has limited capacity to take willful actions. Typically doctors make these categorizations by observing a patient at the bedside. By this method alone, a patient thought to be vegetative could actually be aware.

"It's really a conundrum. The way that consciousness is typically measured is by basically asking somebody to tell you that they are conscious," Owen says. "So if someone wasn't unconscious but couldn't respond and tell you that, they would be classed as unconscious."

In Owen's team's case study, reported in the September 8, 2006, issue of the journal *Science*, the researchers asked the vegetative patient to

GETTY IMAGES

Magnetic resonance imaging (MRI) is now allowing scientists to read the minds of some brain-damaged patients.

(The Author)

KAREN SCHROCK is a staff writer and editor for *Scientific American Mind*.

imagine herself doing various tasks, including walking through the rooms of her home, while they scanned her brain using fMRI. The resulting images [*see box on opposite page*] showed that her response matched that of healthy test subjects—she understood the commands and intentionally decided to comply.

But analyzing the massive volume of data generated by an fMRI scan takes time. When fMRI was first developed, it took up to several months to interpret one scan. As recently as early 2006, when Owen's team scanned the patient's brain, data analysis took many days. "That eureka moment didn't come as she was lying in the scanner," Owen states. "Two weeks later we realized she had indeed been playing tennis in her head."

Now, Owen reports, fMRI technology has advanced to the point where researchers can interpret the data from a scan in 30 or 40 seconds. This breakthrough opens up the possibility of "reading" a person's thoughts at a given moment, enabling a locked-in patient to "speak" with only his or her mind.

New Therapies

Owen and his colleagues hope that one day the new fMRI techniques they are developing will assist doctors in determining which patients are aware but trapped in an unresponsive body, thereby providing a more reliable indication of patients' potential for recovery. The researchers report that their patient who played tennis in her head subsequently improved from her seemingly vegetative state. Owen points out that by scanning her brain with fMRI, doctors were able to tell she was recovering long before she showed any outward physical signs. Early detection of a brain-damaged patient's potential for recuperation could lead to alternative treatments in the form of more aggressive drug or surgical interventions and to the encouragement of social interactions, such as visits from family members.

Owen's team is currently devising a protocol for "talking" to a vegetative patient's mind, by employing the same basic principles as in its initial test of the tennis player. "If the patient imagines playing tennis, it means 'yes.' If they imagine walking through the rooms of their home, it means 'no,'" Owen says. The different thoughts light up, or activate, various regions in the brain. With some practice on healthy subjects, the researchers have learned to tell apart thought-only responses of "yes" and "no" in under a minute. The doctors are now preparing to test their technique on a vegetative patient whom they have already found to be aware. If they succeed, they will "converse" with a locked-in person for the first time ever.

As with any new technology, it will take several years to understand how best to use fMRI in a clinical setting, and for now, researchers continue to deny most requests to scan brain-damaged patients. "It's not ethical, because we have not completed the research we would need to complete to be absolutely certain that our inter-

Glossary of Consciousness

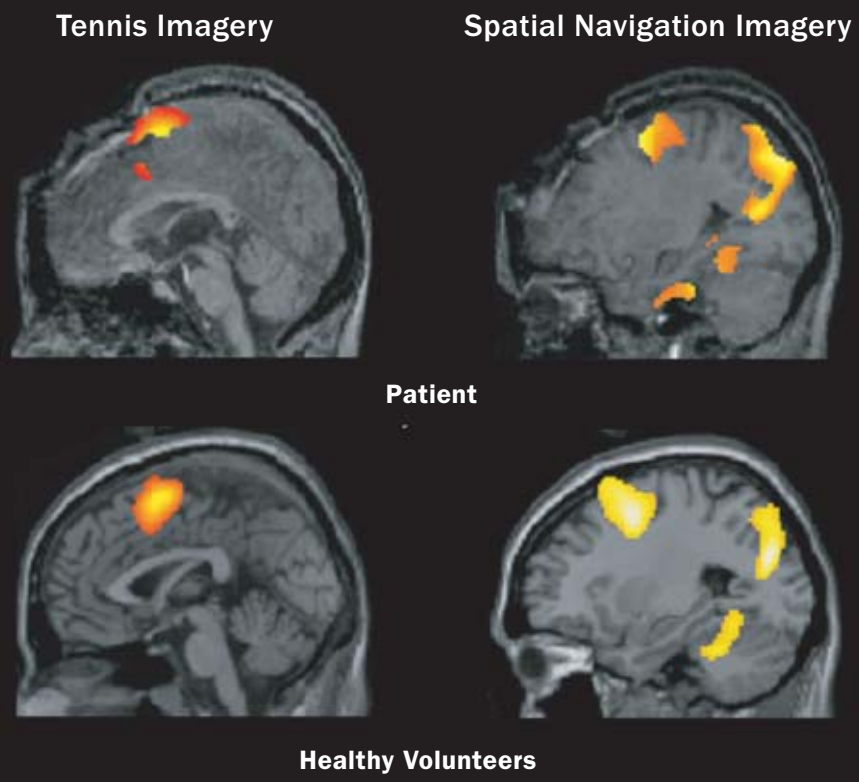
ELLEN CAREY *Getty Images*

Doctors define consciousness as having two important components: wakefulness and awareness. Disorders of consciousness are diagnosed when one or both of these elements are impaired.

DIAGNOSIS	AWAKE	AWARE
Coma	No	No
Vegetative state	Yes	No
Minimally conscious state	Yes	Yes, but responsiveness is severely limited

Evidence of Awareness

Researchers discovered that a vegetative patient was actually conscious by comparing her brain activity with that of healthy controls. When the patient and the healthy subjects were asked to imagine playing tennis and walking through the rooms of their homes, their brains showed similar activation in motor and spatial navigation areas.



pretations of the scan are right," says Hirsch, who fields e-mails from concerned family members on a daily basis. "It's just heart-wrenching, the number of people out there who want to know about the cognitive life of their loved ones who can't respond to them."

For now, using fMRI to diagnose or communicate with brain-damaged patients will continue to happen only in the small number of research laboratories devoted to studying disorders of consciousness. Funding is scarce for investigators studying brain damage, according to both Hirsch and Owen. The equipment is expensive—a state-of-the-art MRI scanner capable of functional scanning costs several million dollars—and scientists have not yet figured out the best way to use the relatively new technology. But with the possibility of being able to communicate with vegetative patients lurking just on the horizon, the researchers hope their work will eventually lead to the widespread release of locked-in minds.

"It's not something that every hospital can start doing yet," Owen says. "But we'd like to develop the technique so we can make it easier and accessible to everyone." M

(Further Reading)

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The PAIN GATE

A rare disorder brings insights into the nature of pain

By David Dobbs

For most of the 140 years since it was named, the disorder known as burning man syndrome has operated in near-total obscurity. Even today it afflicts perhaps 200 to 500 people in all of North America and a few thousand worldwide. Until about three years ago, essentially all medical knowledge about it was contained in its name, erythromelalgia, which translates as "painful red extremities." Few doctors knew of it, only a handful had seen it, and none knew what caused it or how to treat it. At any given time, the few thousand people who had it suffered its torment—searing heat in the feet and lower legs and sometimes in the hands—without understanding why. Most thought they were completely alone.

HIROSHI HIGUCHI *Getty Images*

The pain comes in a bewildering variety—shooting, burning, stabbing, electrical-like.

Pam Costa is one of only a handful of people in the U.S. with an inherited form of erythromelalgia. Gene clues from families such as hers have helped researchers pin down the mutation involved.

Pam Costa, 42, lived her first decade this way. She is one of perhaps 30 or 40 people in the U.S., and possibly 200 to 500 worldwide, known to have an inherited form of the disease.

"In the crib I would pull myself up and hang my hands over the side and just scream," Costa says. "My first word, I'm told, was 'hands,' because they were hot.

"Later, when I was in school—I grew up in southern California, and it was hot—my feet burned all the time. I frequently had to stick them in the toilet. I couldn't understand how other people could wear shoes and socks. And gym—gym was torture. I remember once we had to run track. I ran as far as I could, until the burning was shooting all up my legs, and then I fell down. They sent me to the office for trying to get out of gym.

"No one had any idea what it was. I didn't even know it had a name."

In 1976, when Costa was 10 years old, her family received a letter from a team of researchers at the University of Alabama. At the time Costa was missing most of fifth grade. Walking to and around school inflamed her legs, and her hands hurt too much to hold a pen.

The researchers' letter shed some light on this condition. The university was assembling the pedigree of an Alabama family that had several members with something called erythromelalgia, or EM, a poorly understood disorder that in this family's case seemed to be hereditary. The family tree appeared to include Costa and her mother. Did either of them ever experience burning sensations in her feet or hands?

That letter, Costa says, "was just huge. It's not like it erased the problem. But I could start to grapple with it as a thing outside of me." With help from a remarkable sixth grade teacher, Sally Jackson ("the first one," Costa says, "to notice I did 'A' work when the weather was cool"), Costa began to confront and manage her condition instead of succumbing to it. She brought ice packs to school, got released from gym to read, learned to recognize what she could and could not do, and learned she could make all A's instead of mostly D's. She went to college and then graduate school, earning a Ph.D. in psychology. She married, opened a practice, started teaching and, five years ago, adopted a daughter—all, Costa says, made possible "by Sally Jackson and by that letter 30 years ago." By naming and rationalizing her condition, the letter made it finite. And the finite, however big and ugly, could be approached.

Costa never expected another insight with that sort of power. Yet 28 years later, in September 2004, one came—this one via an e-mail from the Erythromelalgia Association, a research and support group she had joined. A team of pain researchers at the Yale University School of Medicine, building on a Beijing team's discovery of a genetic mutation underlying inherited erythromelalgia, had not only confirmed this genetic basis but had also discovered what appeared to be EM's prime physiological mechanism. A defective sodium channel in pain-sensing neurons in the legs and arms—a door, essentially, through which pain signals are sent to the brain—was too quick to open and too slow to close. When this door was open, pain rushed through like fire. But it was a door, the research suggested, that might someday be shut.

A Rootless Pain

Stephen Waxman, chair of neurology at Yale and head of the lab that published the sodium channel paper, is a man who likes a bit of history.

CHRIS COSTA

FAST FACTS

Pain That Won't Stop

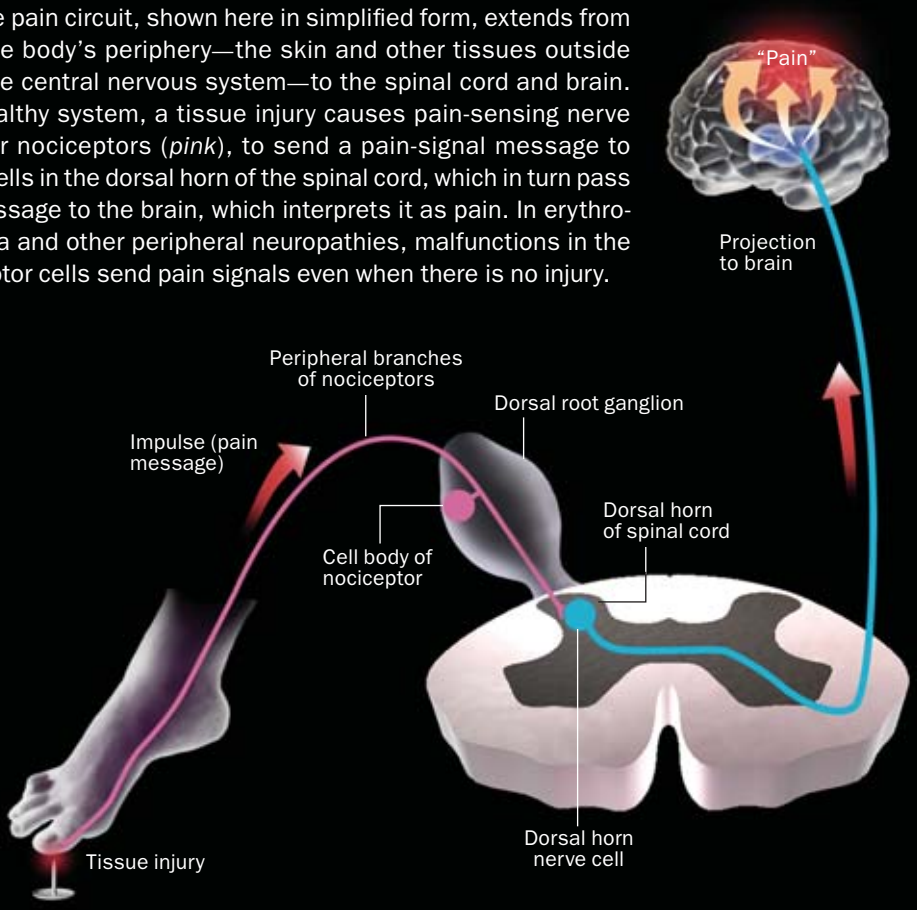
1» People who suffer from a rare disorder called burning man syndrome, or erythromelalgia, experience searing pain in the feet and lower legs and sometimes in the hands.

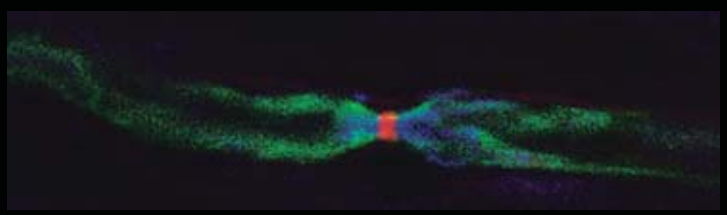
2» Investigators recently uncovered erythromelalgia's prime physiological mechanism. A defect in a sodium channel in pain-sensing neurons in the legs and arms makes the neurons overexcitable: they overreact, sending signals of blazing pain even in the absence of tissue damage.

3» Finding the flaw in this "pain gate" brings hope that researchers will learn how to shut off the searing signals.

Feeling the Pain

The pain circuit, shown here in simplified form, extends from the body's periphery—the skin and other tissues outside the central nervous system—to the spinal cord and brain. In a healthy system, a tissue injury causes pain-sensing nerve cells, or nociceptors (*pink*), to send a pain-signal message to nerve cells in the dorsal horn of the spinal cord, which in turn pass the message to the brain, which interprets it as pain. In erythromelalgia and other peripheral neuropathies, malfunctions in the nociceptor cells send pain signals even when there is no injury.





Sodium channels (*red*) are seen in a mouse nerve. In people with the chronic pain disorder erythromelalgia, similar channels in peripheral neurons are overexcitable, amplifying pain messages.

AMADEO BACHAR (*top*); FROM "INTEGRATION OF ENGRAFTED SCHWANN CELLS INTO INJURED PERIPHERAL NERVE: AXONAL ASSOCIATION AND NODAL FORMATION ON REGENERATED AXONS," BY CHRISTINE RADTKE ET AL., IN *NEUROSCIENCE LETTERS*, VOL. 387; © 2005, REPRINTED WITH PERMISSION FROM ELSEVIER (*bottom*)

When the Beijing paper drew his attention to erythromelalgia (although Waxman sees a diverse group of patients, he had never seen someone with EM) he soon took an opportunity to dig through the archives of the man who first named the disorder, Silas Weir Mitchell. It proved an illuminating dig.

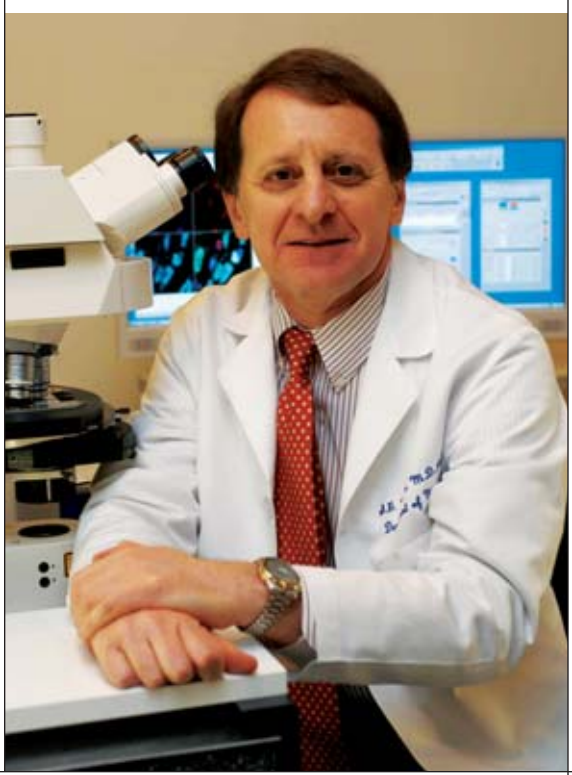
Mitchell, the son of a rich Philadelphia doctor, began his medical career "wanting," his own father said, "in nearly all the qualities that go to make a success in medicine." He ended it as one of the century's leading neurologists. The transformation was attributed mainly to the Civil War, during which Mitchell directed a 400-bed military hospital for nervous injuries and diseases in Philadelphia. Among the hundreds of neurological problems he saw there were three that he first described and defined. One was erythromelalgia. The other two were phantom limb, which is the sensation of retaining one's amputated appendage, and causalgia, a burning pain that sets in near a wound site after the wound is repaired and seems to have healed.

Phantom limb and causalgia result exclusively

A pain circuit in the body holds many relay switches. Where was the open one?

from trauma; erythromelalgia, not so. Yet Waxman, reading Mitchell's patient accounts and correspondence, could see why Mitchell would single out erythromelalgia as a separate but related entity. All three come from mysterious mechanisms (phantom pain is still poorly understood today). All three fall into the broad class of disorders known as peripheral neuropathies, in which numbness, poor function or pain, usually in the limbs (and thus in the "periphery"), arises not from active injury but from malfunctions in the sensory nerve fibers running from tissue to brain. Peripheral neuropathy can cause anything from numb toes to carpal tunnel syndrome to paralysis.

Often it causes pain. The pain assumes a bewildering variety of manifestations—shooting, burning, stabbing, electrical-like—and usually affects feet or hands. Some patients, like Mitchell's soldiers, develop neuropathies after experiencing injury or surgery. Many more suffer "secondary" neuropathies that accompany inflammatory or immunological disorders or diseases such as hypertension, AIDS, cancer, diabetes or multiple sclerosis. An estimated 50 million people in the U.S. alone have a form of neuropathy. Some 10 million to 20 million of them suffer pain.



Stephen Waxman, chair of neurology at Yale University, seeks to understand the roots of pain.

BILL FITZ-PATRICK

"Virtually all chronic pain is neuropathic pain," Waxman says. "My dad had severe neuropathic pain from diabetes. Toward the end only opiates would help. Awful."

Waxman and other researchers have tried for years to understand these pains, hoping to cure them and to reveal their fundamental mechanisms: if pain is a signal received, then study faulty signals. And what better signals to study than the exaggerated ones coming from neuropathies? Work as early as the 1950s showed that motor neurons damaged in trauma often emit exaggerated signals for weeks afterward. By the 1980s comparable malfunction was confirmed in sensory neurons, and this kind of sustained hyperexcitability, as if a relay switch were left on by accident, became the focal point of chronic pain research.

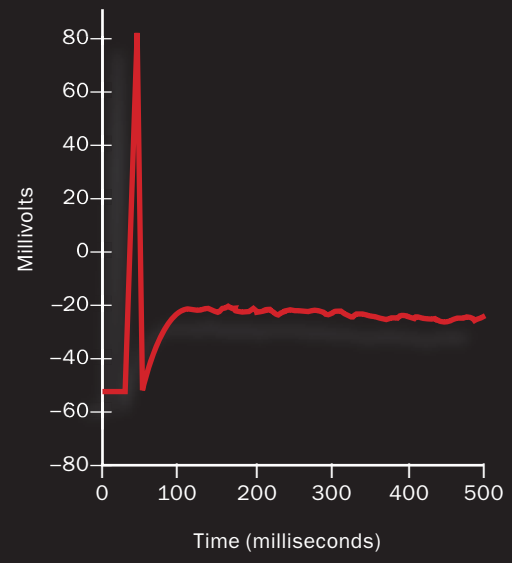
But a pain circuit holds many switches. Where was the open one? Sodium channels made the short list early. British physiologists Alan L. Hodgkin and Andrew F. Huxley established the existence and transmission role of sodium channels in 1952 by recording currents from the giant axon of an Atlantic squid. Subsequent research confirmed that sodium channels (along with calcium, potassium and other ion channels) transmit signals in many types of cells, including muscle, motor neurons and cardiac tissue. But sodium channels serve particularly vital roles in the nervous system. By releasing positively charged sodium ions through the walls of axon fibers, they create the electrical impulses—the action potentials—that start the electrochemical process by which neurons send signals.

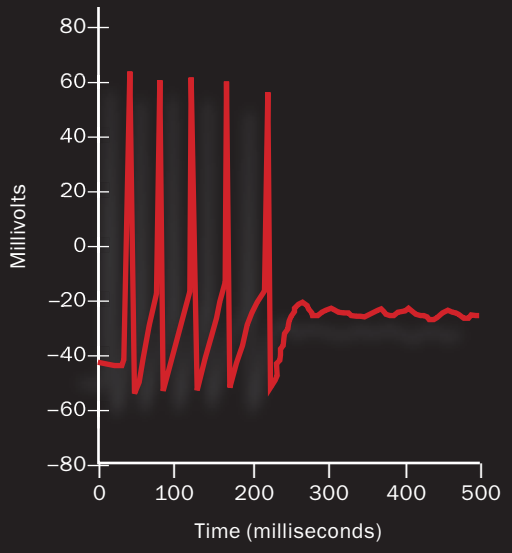
By 1990 Waxman and many other researchers had produced a pile of studies suggesting that problems associated with sodium channels, "channelopathies," might underlie neuropathic pain. But these studies, as Waxman lamented in a 1999 literature review, "did not examine the crucial question: What type(s) of sodium channels produce the … discharge associated with pain?" There were nine sodium channels altogether. Which ones were at fault?

Even as Waxman posed that question, his team was acquiring new tools of gene manipulation and observation that would help them answer it. Now they could examine an overexcited axon's various sodium channels and see which ones had genes that were behaving oddly—build-

The Gate Stays Open

Pain-sensing ends of nociceptor neurons contain ion channels called $Na_v1.7$ sodium channels—the "gateways" to nerve-cell response. A neuron with normal $Na_v1.7$ channels "fires" once in response to an electrical stimulus (*left*). In contrast, the L858H mutation results in a hyperexcitable neuron—causing sustained pain signal (*right*).





ing proteins (and thus setting off activity) when they should be dormant, for instance, or lying dormant when they should be busy. Over years of work they and others narrowed the field. To Waxman and his lab mates (as well as some researchers elsewhere), the results increasingly implicated the seventh of the nine channels, $Na_v1.7$. They call it One Seven.

They got good at creating overexcitable One Sevens. But they could not find a way to block the activity of One Seven within complete pain systems, and that meant that they could not confirm its role by absence. (The easiest way to confirm the role of a light switch is to flip it and turn off the light.) Another way to confirm its role would be to identify the particular gene underlying its odd behavior. Unfortunately, an injured neuron reacts by flipping switches on hundreds of genes, firing them up to build the proteins that send signals and repair things. They faced a needle-in-haystack situation.

"What we needed," Waxman says, "was a genetic change within the sodium channel—presumably One Seven—that we knew was isolated. In short, we needed a mutation.

"I actually said to the team, 'You know, sometimes rare genetic diseases can produce this sort of effect.' But … well, they're rare. Most neurologists go through an entire career and never see a neuropathic problem that's genetic. None of us had ever seen one. No one in this state had. But that's what we needed. We needed a family."

Haunted by Pain

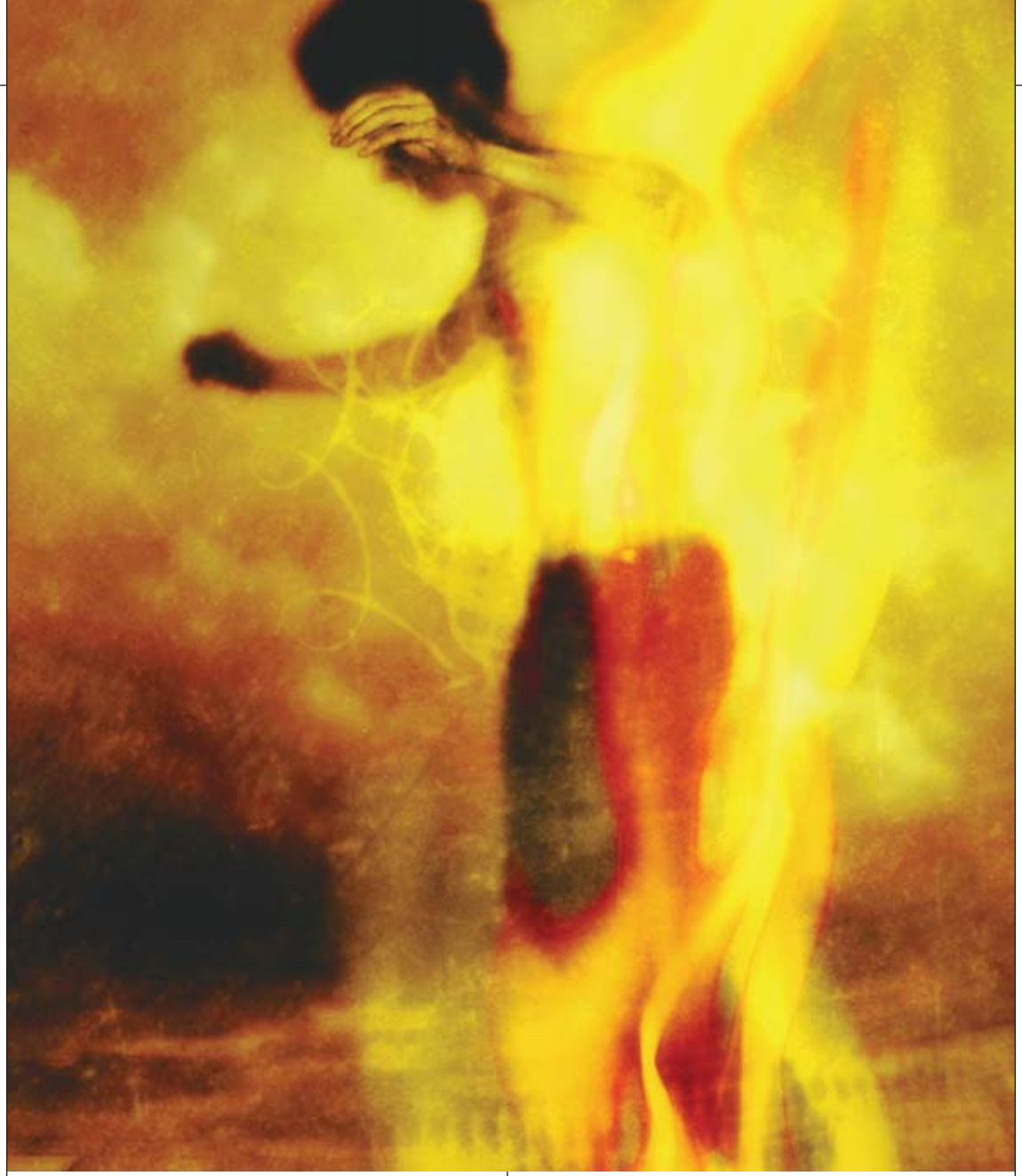
While talking to Pam Costa one evening, I asked her if her condition was worsening, as EM often does. She said it was. She had roughly doubled her pain medications in the past five years or so and was now taking about eight to 10 aspirin a day, another six to eight naproxen (a pain reliever and anti-inflammatory drug) and 90 milligrams of sustained-release morphine, and she still sometimes woke in so much pain that her husband had to give her a morphine injection. And the bad stretches seemed to get longer. She had recently experienced one that lasted 17 days. "I had a friend who saw part of a shorter one," she said. "She asked me how I went 17 days. I get through it because I always tell myself that it will end. And it always does.

"I should make it clear that I consider myself extraordinarily fortunate. I have two arms and legs, and they work. This [condition] has never

(The Author)

DAVID DOBBS (www.daviddobbs.net) is a contributing editor for *Scientific American Mind* and editor of its Mind Matters blog (www.sciammind.com).

FROM "A SINGLE SODIUM CHANNEL MUTATION PRODUCES HYPER- OR HYPOEXCITABILITY IN DIFFERENT TYPES OF NEURONS," BY ANTHONY M. RUSH, SULAYMAN D. DIB-HAJJ, SHUJUN LIU, THEODORE R. CUMMINS, JOEL A. BLACK AND STEPHEN G. WAXMAN, IN *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCE USA*, VOL. 103, NO. 2: MAY 23, 2006



KAMIL VOJNAR *Getty Images*

stopped me from pursuing my goals. I have a fabulous family. I've worked with so many people who have suffered more."

At this point she paused. Over the phone, 3,000 miles away, I could tell she was considering whether to continue.

"I have a young cousin," she said. "When Jacob [a pseudonym] was two, he was in so much pain they started giving him morphine. At first they thought he had autism, because he couldn't seem to learn anything or relate to anyone. But a rheumatologist who examined him said he was in so much pain he just couldn't take anything in. I saw Jacob a year ago, when he was three. He was not walking.

"Jacob's mother is missing, probably an opiate addict. Too much pain. His grandmother committed suicide because of the pain. Jacob is being raised by his great-grandmother, who's in her 80s."

Hidden in Plain Sight

One of the many oddities of this story is that although Stephen Waxman knew about erythromelalgia and even knew it had an inherited form, he did not know of the University of Alabama study and so knew nothing of Pam Costa's family. Nor did anyone in his laboratory, nor did the many colleagues with whom he inquired about familial neuropathies. This may seem a bit strange—and it is. It reflects the weird obscurity that erythromelalgia retained until 2004. Despite 25 years of increasing recognition that most chronic pain arises from neuropathy, this singu-

larly mysterious neuropathy never crossed the path of the pain research community.

"These people got sent everywhere else," Waxman says. "They got referred to dermatologists, vascular specialists, hematologists, cardiologists, rheumatologists—everybody but neurologists."

This disconnect ended in March 2004, when Waxman spotted in the *Journal of Medical Genetics* a paper titled "Mutations in SCN9A, Encoding a Sodium Channel Alpha Subunit, in Patients with Primary Erythermalgia." The authors, a team of dermatologists and geneticists in Beijing, had analyzed the genetic profiles of two relatives with inherited EM and ferreted out the faulty gene.

That was sharp work. But because the Chinese authors were dermatologists and geneticists, Waxman notes, "They did not know an important thing"—specifically, that the sodium channel encoded by the mutation they had discovered operates almost exclusively in peripheral pain-sensing neurons. Dermatologists unaware of that would naturally try to find the channel doing its work in skin. But they would not find it. It was a neuron-specific channel.

The channel in question was $Na_v1.7$. Waxman's lab certainly knew where to look for it.

"In neuroscience," Waxman explains, "it's standard fare if you find a mutation in an ion channel to clone it into some fresh cells and see what effect the mutation has. Normally it would take a year of tough work to clone a channel like that. But as it happened, we had the construct right here on the shelf. It took us two months.

"It was as we expected. The mutations lowered One Seven's activation threshold. They created overactive channels that amplify and sustain. When they're supposed to be quiet, they talk. When they're supposed to whisper, they scream."

Since Waxman's lab published the results in September 2004, it and others have confirmed and elaborated on the fact that certain mutations at SCN9A (they have identified seven so far) create a malfunction at $Na_v1.7$ that causes erythromelalgia. In December 2006 a University of Cambridge team reported an SCN9A mutation that created a complete *lack* of pain sensation. They found the mutation in the family of a 10-year-old street entertainer in Pakistan who wowed crowds by walking on hot coals and stabbing himself through the arm. He later died falling off a roof.

Waxman now knows scores of people with EM, including Costa, who provided a blood sample, complete with a mutation at SCN9A, for one of his studies. More families have emerged. A couple of times a month he gets an e-mail from a patient he did not know about. Most are wrenching. "Keeps us going," Waxman says, "when the experiments don't work."

"A lot of them ask," Waxman tells me toward the end of our visit, " 'When might you have a cure?' I don't mean to say they're impatient. They're not. They're remarkably generous-minded. But everyone needs to understand we're really still discerning fundamental biology here. And these things take a lot of time. If Merck or Abbott found on its shelves *today* a drug that quieted One Seven in a lab assay, it could still take 10 years. And this is pretty challenging biology."

> "I get through it because I always tell myself that it will end. And it always does."

On the plus side, notes Sulayman Dib-Hajj, Waxman's genetics specialist, $Na_v1.7$ makes a pretty good drug target. It appears to do little besides sending pain, so dampening it may cause few side effects. And "it expresses beautifully," generally responding to experimental manipulation in unambiguous ways, Dib-Hajj says.

"In the meantime," Dib-Hajj observes, "I like to think that patients find it helpful to know a bit more about what they have. I mean, sometimes pain is in your head. But here it's not. It's in your sodium channels."

When I tell Pam Costa about this, she laughs. "It's true!" she says. "I've *always* found it helps to think some particular physiological process was causing this. Now I have the process. I can visualize those sodium channels overacting, all those ions flowing through, and I think very hard about slowing them down." M

(Further Reading)

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- The Erythromelalgia Association provides more research information at **www.erythromelalgia.org**

We blame teen turmoil on immature brains. But did the brains cause the turmoil, or did the turmoil shape the brains?

The Myth of the Teen Brain

By Robert Epstein

It's not only in newspaper headlines—it's even on magazine covers. *TIME*, *U.S. News & World Report* and even *Scientific American Mind* have all run cover stories proclaiming that an incompletely developed brain accounts for the emotional problems and irresponsible behavior of teenagers. The assertion is driven by various studies of brain activity and anatomy in teens. Imaging studies sometimes show, for example, that teens and adults use their brains somewhat differently when performing certain tasks.

As a longtime researcher in psychology and a sometime teacher of courses on research methods and statistics, I have become increasingly concerned about how such studies are being interpreted. Although imaging technology has shed interesting new light on brain activity, it is dangerous to presume that snapshots of activity in certain regions of the brain necessarily provide useful information about the causes of thought, feeling and behavior.

PETER DAZELEY *Getty Images*

If the "teen brain" were a universal phenomenon, we would find teen turmoil around the world.

This fact is true in part because we know that an individual's genes and environmental history—and even his or her own behavior—mold the brain over time. There is clear evidence that any unique features that may exist in the brains of teens—to the limited extent that such features exist—are the *result* of social influences rather than the *cause* of teen turmoil. As you will see, a careful look at relevant data shows that the teen brain we read about in the headlines—the immature brain that supposedly causes teen problems—is nothing less than a myth.

Cultural Considerations

The teen brain fits conveniently into a larger myth, namely, that teens are inherently incompetent and irresponsible. Psychologist G. Stanley Hall launched this myth in 1904 with the publication of his landmark two-volume book *Adolescence*. Hall was misled both by the turmoil of his times and by a popular theory from biology that later proved faulty. He witnessed an exploding industrial revolution and massive immigration that put hundreds of thousands of young people onto the streets of America's burgeoning cities. Hall never looked beyond those streets in formulating his theories about teens, in part because he believed in "recapitulation"—a theory from biology that asserted that individual development (ontogeny) mimicked evolutionary development (phylogeny). To Hall, adolescence was the necessary and inevitable reenactment of a "savage, pigmoid" stage of human evolution. By the 1930s the recapitulation theory was completely discredited in biology, but some psychologists and the general public never got the message. Many still believe, consistent with Hall's assertion, that teen turmoil is an *inevitable* part of human development.

Today teens in the U.S. and some other Westernized nations do display some signs of distress. The peak age for arrest in the U.S. for most crimes has long been 18; for some crimes, such as arson, the peak comes much earlier. On average, American parents and teens tend to be in conflict with one another 20 times a month—an extremely high figure indicative of great pain on both sides. An extensive study conducted in 2004 suggests that 18 is the peak age for depression among people 18 and older in this country. Drug use by teens, both legal and illegal, is clearly a problem here, and suicide is the third leading cause of death among U.S. teens. Prompted by a rash of deadly school shootings over the past decade, many American high schools now resemble prisons, with guards, metal detectors and video monitoring systems, and the high school dropout rate is nearly 50 percent among minorities in large U.S. cities.

But are such problems truly inevitable? If the turmoil-generating "teen brain" were a universal developmental phenomenon, we would presumably find turmoil of this kind around the world. Do we?

In 1991 anthropologist Alice Schlegel of the University of Arizona and psychologist Herbert Barry III of the University of Pittsburgh reviewed research on teens in 186 preindustrial societies. Among the important conclusions they drew about these societies: about 60 percent had no word for "adolescence," teens spent almost all their time with adults, teens showed almost no signs of psychopathology, and antisocial behavior in young males was completely absent in more than half these cultures and

FAST FACTS

Troubled Teens

1» Various imaging studies of brain activity and anatomy find that teens and adults use their brains somewhat differently when performing certain tasks. These studies are said to support the idea that an immature "teen brain" accounts for teen mood and behavior problems.

2» But, the author argues, snapshots of brain activity do not necessarily identify the *causes* of such problems. Culture, nutrition and even the teen's own behavior all affect brain development. A variety of research in several fields suggests that teen turmoil is caused by cultural factors, not by a faulty brain.

3» Anthropological research reveals that teens in many cultures experience no turmoil whatsoever and that teen problems begin to appear only after Western schooling, movies and television are introduced.

4» Teens have the potential to perform in exemplary ways, the author says, but we hold them back by infantilizing them and trapping them in the frivolous world of teen culture.

CATHERINE LEDNER *Getty Images*

In many Western cultures, teens socialize almost exclusively with other teens.

extremely mild in cultures in which it did occur.

Even more significant, a series of long-term studies set in motion in the 1980s by anthropologists Beatrice Whiting and John Whiting of Harvard University suggests that teen trouble begins to appear in other cultures soon after the introduction of certain Western influences, especially Western-style schooling, television programs and movies. Delinquency was not an issue among the Inuit people of Victoria Island, Canada, for example, until TV arrived in 1980. By 1988 the Inuit had created their first permanent police station to try to cope with the new problem.

Consistent with these modern observations, many historians note that through most of recorded human history the teen years were a relatively peaceful time of transition to adulthood. Teens were not trying to break away from adults; rather they were learning to *become* adults. Some historians, such as Hugh Cunningham of the University of Kent in England and Marc Kleijwegt of the University of Wisconsin–Madison, author of *Ancient Youth: The Ambiguity of Youth and the Absence of Adolescence in Greco-Roman Society* (J. C. Gieben, 1991), suggest that the tumultuous period we call adolescence is a very recent phenomenon—not much more than a century old.

My own recent research, viewed in combination with many other studies from anthropology, psychology, sociology, history and other disciplines, suggests the turmoil we see among teens in the U.S. is the result of what I call "artificial extension of childhood" past the onset of puberty. Over the past century, we have increasingly infantilized our young, treating older and older people as children while also isolating them from adults and passing laws to restrict their behavior [*see box on next page*]. Surveys I have conducted show that teens in the U.S. are subjected to more than 10 times as many restrictions as are mainstream adults, twice as many restrictions as active-duty U.S. Marines, and even twice as many restrictions as incarcerated felons. And research I conducted with Diane Dumas as part of her dissertation research at the California School of Professional Psychology shows a positive correlation between the extent to which teens are infantilized and the extent to which they display signs of psychopathology.

The headlines notwithstanding, there is no question that teen turmoil is *not* inevitable. It is

a creation of modern culture, pure and simple—and so, it would appear, is the brain of the troubled teen.

Dissecting Brain Studies

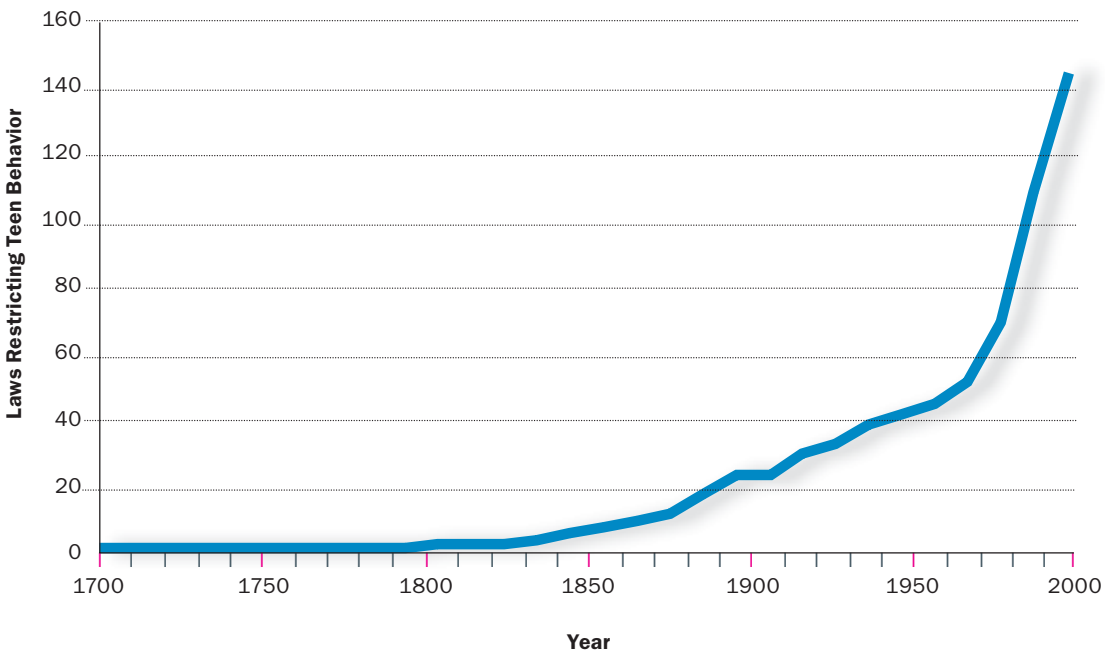
A variety of recent research—most of it conducted using magnetic resonance imaging (MRI) technology—is said to show the existence of a teen brain. Studies by Beatriz Luna of the department of psychiatry at the University of Pittsburgh, for example, are said to show that teens use prefrontal cortical resources differently than adults do. Susan F. Tapert of the University of California, San Diego, found that for certain memory tasks, teens use smaller areas of the cortex than adults do. An electroencephalogram (EEG) study by Irwin Feinberg and his colleagues at the University of California, Davis, shows that delta-wave activity during sleep declines in the early teen years. Jay Giedd of the National Institute of Mental Health and other researchers suggest that the decline in delta-wave activity might be related to synaptic pruning—a reduction in the number of interconnections among neurons—that occurs during the teen years.

This work seems to support the idea of the teen brain we see in the headlines until we realize two things. First, most of the brain changes that are observed during the teen years lie on a continuum of changes that take place over much of our lives. For example, a 1993 study by Jésus Pujol and his colleagues at the Autonomous University of Barcelona looked at changes in the corpus callosum—a massive structure that connects the two sides of the brain—over a two-year period with individuals between 11 and 61 years old. They found that although the rate of growth declined as people aged, this structure still grew by about 4 percent each year in people in their 40s (compared with a growth rate of 29 percent in their youngest subjects). Other studies, conducted by researchers such as Elizabeth Sowell of the University of California, Los Angeles, show that gray matter in the brain continues to disappear from childhood well into adulthood.

Second, I have not been able to find even a single study that establishes a *causal* relation between the properties of the brain being examined and the problems we see in teens. By their very nature, imaging studies are correlational, showing simply that activity in the brain is associated with certain behavior or emotion.

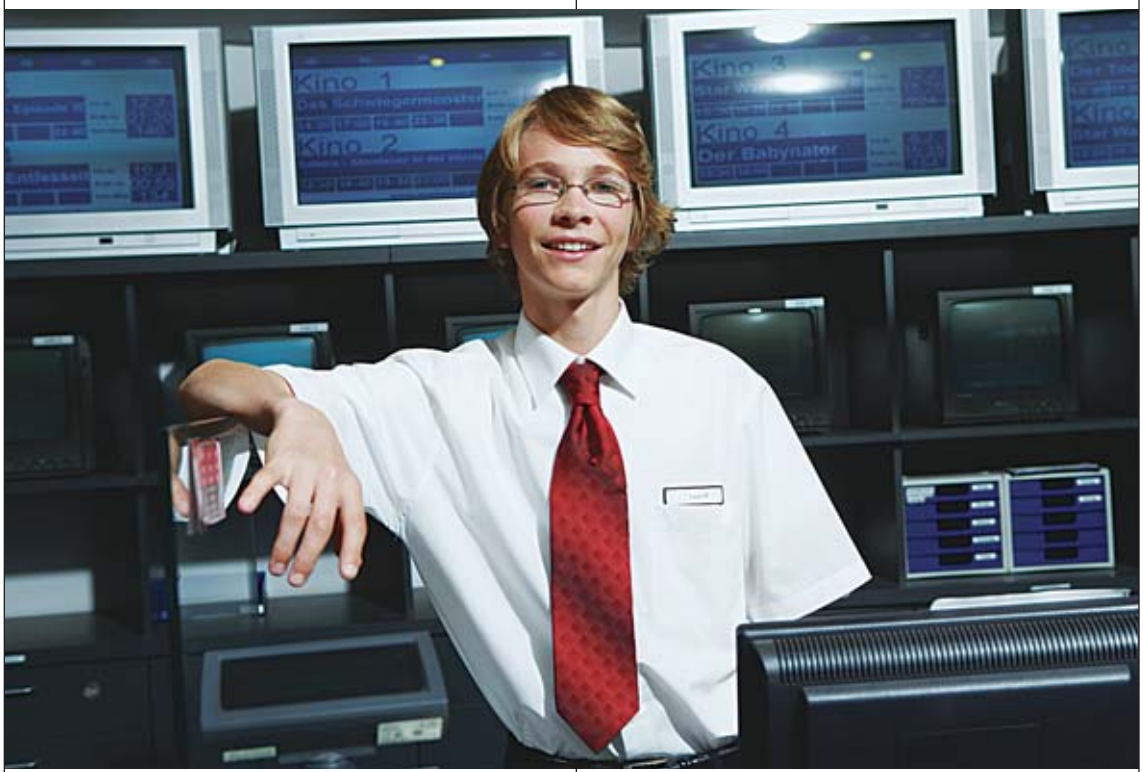
Rebels with a Cause

Laws restricting the behavior of young people (under age 18) have grown rapidly in the past century, according to a survey by the author. He found that U.S. teens have 10 times as many restrictions as adults, twice as many as active-duty U.S. Marines and twice as many as incarcerated felons.



SOURCE: *THE CASE AGAINST ADOLESCENCE*, BY ROBERT EPSTEIN (QUILL DRIVER BOOKS, 2007)

Studies of intelligence, perception and memory show that teens are in many ways superior to adults.



ERIK DREYER Getty Images

Young people have extraordinary potential that is often not expressed because teens are infantilized and isolated from adults.

As we learn in elementary statistics courses, correlation does not even imply causation. In that sense, no imaging study could possibly identify the brain as a causal agent, no matter what areas of the brain were being observed.

Is it ever legitimate to say that human behavior is caused by brain anatomy or activity? [See "Brain Scans Go Legal," by Scott T. Grafton, Walter P. Sinnott-Armstrong, Suzanne I. Gazzaniga and Michael S. Gazzaniga; SCIENTIFIC AMERICAN MIND, December 2006/January 2007.] In his 1998 book *Blaming the Brain*, neuroscientist Elliot Valenstein deftly points out that we make a serious error of logic when we blame almost any behavior on the brain—especially when drawing conclusions from brain-scanning studies. Without doubt, all behavior and emotion must somehow be reflected (or "encoded") in brain structure and activity; if someone is impulsive or lethargic or depressed, for example, his or her brain must be wired to reflect those behaviors. But that wiring (speaking loosely) is not necessarily the cause of that behavior or emotion.

Considerable research shows that a person's emotions and behavior continuously change brain anatomy and physiology. Stress creates hypersensitivity in dopamine-producing neurons that persists even after they are removed from the brain. Enriched environments produce more neuronal connections. For that matter, meditation, diet, exercise, studying and virtually all other activities alter the brain, and a new study shows that smoking produces brain changes similar to those produced in animals given heroin, cocaine or other addictive drugs. So if teens are in turmoil, we will necessarily find some corresponding chemical, electrical or anatomical properties in the brain. But did the brain cause the turmoil, or did the turmoil alter the brain? Or did some other factors—such as the way our culture treats its teens—cause both the turmoil and the corresponding brain properties?

(The Author)

ROBERT EPSTEIN is a contributing editor for *Scientific American Mind* and the former editor in chief of *Psychology Today*. He received his Ph.D. in psychology from Harvard University and is a longtime researcher and professor. His latest book is called *The Case Against Adolescence: Rediscovering the Adult in Every Teen* (Quill Driver Books, 2007). More information is at www.thecaseagainstadolescence.com.

Elected achievers: Sam Juhl, 18, mayor of Roland, Iowa (*right*), and Michael Sessions, now 19, mayor of Hillsdale, Mich. (*below*).

ANDREW RULLESTAD *The Ames Tribune/AP Photo (top)*; BILL PUGLIANO *Getty Images News (bottom)*

Unfortunately, news reports—and even the researchers themselves—often get carried away when interpreting brain studies. For instance, a 2004 study conducted by James Bjork and his colleagues at the National Institute on Alcohol Abuse and Alcoholism, at Stanford University and at the Catholic University of America was said in various media reports to have identified the biological roots of teen laziness. In the actual study, 12 young people (ages 12 to 17) and 12 somewhat older people (ages 22 to 28) were monitored with an MRI device while performing a simple task that could earn them money. They were told to press a button after a short anticipation period (about two seconds) following the brief display of a symbol on a small mirror in front of their eyes. Some symbols indicated that pressing the button would earn money, whereas others indicated that failing to respond would cost money. After the anticipation period, subjects had 0.25 second to react, after which time information was displayed to let them know whether they had won or lost.

Areas of the brain that are believed to be involved in motivation were scanned during this session. Teens and adults were found to perform equally well on the task, and brain activity differed somewhat in the two groups—at least during the anticipation period and when $5 (the maximum amount that could be earned) was on the line. Specifically, on those high-payment trials the average activity of neurons in the right nucleus accumbens—but not in other areas that were being monitored—was higher for adults than for teens. Because brain activity in the two groups did not differ in other brain areas or under other payment conditions, the researchers drew a very modest conclusion in their article: "These data indicate qualitative similarities overall in the brain regions recruited by incentive processing in healthy adolescents and adults."

But according to the Long Island, N.Y., newspaper *Newsday*, this study identified a "biological reason for teen laziness." Even more disturbing, lead author James Bjork said that his study "tells us that teenagers love stuff, but aren't as willing to get off the couch to get it as adults are."

In fact, the study supports neither statement. If you truly wanted to know something about the brains of lazy teens, at the very least you would have to have some lazy teens in your study. None were identified as such in the Bjork study. Then you would have to compare the brains of those teens with the brains of industrious teens, as well

as with the brains of both lazy and industrious adults. Most likely, you would then end up finding out how, on average, the brains in these four groups differed from one another. But even this type of analysis would not allow you to conclude that some teens are lazy "because" they have faulty brains. To find out why certain teens or certain adults are lazy (and, perforce, why they have brains that reflect their lazy tendencies), you would still have to look at genetic and environmental factors. A brain-scanning study can shed no light.

Valenstein blames the pharmaceutical industry for setting the stage for overinterpreting the results of brain studies such as Bjork's. The drug companies have a strong incentive to convince public policymakers, researchers, media professionals and the general public that faulty brains underlie all our problems—and, of course, that pharmaceuticals can fix those problems. Researchers, in turn, have a strong incentive to convince the public and various funding agencies that their research helps to "explain" important social phenomena.

The Truth about Teens

If teen chaos is not inevitable, and if such difficulty cannot legitimately be blamed on a faulty brain, just what is the truth about teens? The truth is that they are extraordinarily competent, even if they do not normally express that competence. Research I conducted with Dumas shows, for example, that teens are as competent or virtually as competent as adults across a wide range of adult abilities. And long-standing studies of intelligence, perceptual abilities and memory function show that teens are in many instances far superior to adults.

Visual acuity, for example, peaks around the time of puberty. "Incidental memory"—the kind of memory that occurs automatically, without any mnemonic effort, peaks at about age 12 and declines through life. By the time we are in our 60s, we remember relatively little "incidentally," which is one reason many older people have trouble mastering new technologies. In the 1940s pioneering intelligence researchers J. C. Raven and David Wechsler, relying on radically different kinds of intelligence tests, each showed that raw scores on intelligence tests peak between ages 13 and 15 and decline after that throughout life. Although verbal expertise and some forms of judgment can remain strong throughout life, the extraordinary cognitive abilities of teens, and especially their ability to learn new things rapidly, is beyond question. And whereas brain size is not necessarily a good indication of processing ability, it is notable that recent scanning data collected by Eric Courchesne and his colleagues at the University of California, San Diego, show that brain volume peaks at about age 14. By the time we are 70 years old, our brain has shrunk to the size it had been when we were about three.

Findings of this kind make ample sense when you think about teenagers from an evolutionary perspective. Mammals bear their young shortly after puberty, and until very recently so have members of our species, *Homo sapiens*. No matter how they appear or perform, teens *must* be incredibly capable, or it is doubtful the human race could even exist.

Today, with teens trapped in the frivolous world of peer culture, they learn virtually everything they know from one another rather than from the people they are about to become. Isolated from adults and wrongly treated like children, it is no wonder that some teens behave, by adult standards, recklessly or irresponsibly. Almost without exception, the reckless and irresponsible behavior we see is the teen's way of declaring his or her adulthood or, through pregnancy or the commission of serious crime, of instantly *becoming* an adult under the law. Fortunately, we also know from extensive research both in the U.S. and elsewhere that when we treat teens like adults, they almost immediately rise to the challenge.

We need to replace the myth of the immature teen brain with a frank look at capable and savvy teens in history, at teens in other cultures and at the truly extraordinary potential of our own young people today. M

When we treat teens like adults, they almost immediately rise to the challenge.

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- **The End of Adolescence.** Philip Graham. Oxford University Press, 2004.

Chips in Your Head

Damaged or diseased brains could soon get a boost from implanted prosthetics

By Frank W. Ohl and Henning Scheich

PETER MALTZ *Images.com/Corbis*

As many as 400,000 Americans are partially or totally paralyzed from spinal cord injuries, which interrupt the nerve cell signals relaying information between the brain and the body. Others lose the ability to move and communicate because of neurodegenerative disorders such as amyotrophic lateral sclerosis, or Lou Gehrig's disease, which causes the neurons controlling muscles to die. Still half a million more Americans suffer profound sensory deficits such as blindness or deafness. For more than a century, scientists have sought some type of electrical replacement for lost motor and perceptual functions to alleviate these conditions.

Only recently, however, have researchers and doctors begun testing such neuroprostheses in humans. Existing prosthetic instruments transmit signals from areas in the body to the brain—cochlear implants in the inner ear, for example, can send signals to the auditory nerve to enable hearing. The next generation of devices, however, will move into the brain itself [*see box on page 67*]. Various research teams are now building so-called brain-computer interfaces (BCIs), which help to restore paralyzed patients' ability to communicate and move by translating neuron signals in their brains into commands that control computer cursors or robots. And a new wave of brain implants, including a type developed in our laboratory in Germany, is poised to transfer information *into* the brain, thereby reviving sensory function.

The latest in experimental brain prosthetics enabled a paralyzed person to control a robot.

Making a Move

One class of neuroprosthetics is designed to tap into signals transmitted from paralyzed individuals' working muscles or motor neurons and use them to produce movement in either distant regions of their own body or external devices that they would otherwise be powerless to control. Peripheral devices that read out signals in this manner may connect with nerve fibers that innervate muscles to control hand, arm or leg movements artificially. The NeuroControl Freehand System, a prosthetic device made by NeuroControl Corporation in Cleveland and approved by the Food and Drug Administration, for example, can return some hand movement to quadriplegics by substituting for the neural signals controlling the hand and forearm that were interrupted after nerve damage from a spinal cord injury. A shoulder-position sensor transmits small shoulder movements, via radio waves and implanted wires, to eight electrodes attached to paralyzed hand and forearm muscles. Patients with some residual shoulder mobility can use that motor signal to open and close their opposite hand, allowing them to perform tasks such as picking up mail, changing television channels or eating a sandwich.

Currently under development are systems that enable paralyzed individuals to operate devices existing outside the body, such as computers, by "listening" to the neural murmurs inside the brain itself. In some of these BCIs, scalp electrodes record the electrical waves emanating from groups of millions of brain neurons. Psychologist Niels Birbaumer of the University of Tuebingen in Germany and his colleagues have created something they call a "thought translation device," which converts such brain transmissions into movements of a cursor on a computer screen. Paralyzed volunteers learn to manipulate their thoughts so as to choose between two cursor positions or letters, enabling them to spell out words. In this way, a person who cannot speak or type can communicate through thought alone [see "Thinking Out Loud," by Nicola Neumann and Niels Birbaumer; SCIENTIFIC AMERICAN MIND, December 2004].

Other researchers are devising BCIs that are implanted within the brain to listen in on the chatter produced by either single or small groups of neurons. Several years ago a team headed by Duke University neurobiologist Miguel Nicolelis inserted electrodes in the cerebral cortex of a female owl monkey named Belle. The electrodes recorded neural activity while the animal moved a lever. A computer then transformed the neural signals into commands that were sent through the Internet to operate a robotic arm in a laboratory some 600 miles away. In later experiments, the Duke team has taught monkeys with implanted electrode arrays to operate computer cursors and robotic arms by altering their brain activity without moving at all.

Researchers working under neuroscientist John Donoghue of Brown University recently performed a similar experiment in four people. One of them was Matthew Nagle, a 26-year-old man who was paralyzed from the neck down as a result of a knife injury. Neurosurgeons implanted an array of hair-thin electrodes into Nagle's brain. The electrodes picked up signals from neurons in his motor cortex, the brain region primarily responsible for movement control. These signals were fed to a computer through a pedestal positioned on top of Nagle's head and then translated into the movement of a computer cursor, a prosthetic hand and a robotic arm.

When Nagle simply imagined performing a movement in a particular direction, the computer, robot or hand prosthesis would respond accordingly. Through this method he was able to open simulated e-mail, perform a "pinching" ges-

FAST FACTS

Brain Prosthetics

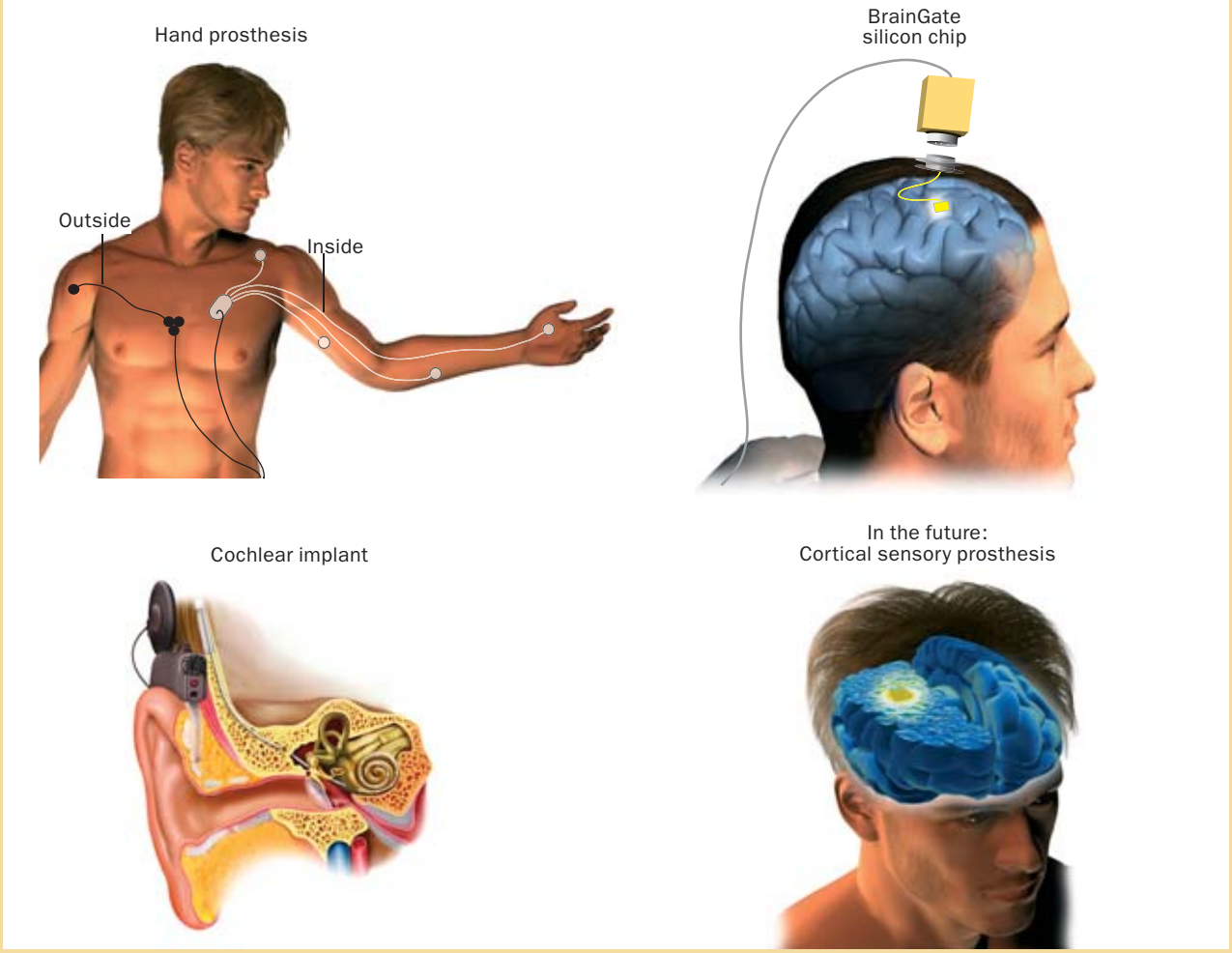
1» Scientists are building devices that help to restore the ability of paralyzed patients to communicate and move by translating neuron signals in their brain into commands that control computer cursors or robots.

2» Now a new wave of brain implants is poised to transfer information *into* the brain, thereby reviving sensory function for patients.

3» With a hearing neuroprosthesis in their brain, deaf gerbils could differentiate between high- and low-frequency tones and changes in interval, as well as more complex sound patterns. The rodents detected these sounds just as well as gerbils that heard them with their ears.

Replacement Parts for the Nervous System

Neuroprostheses may be implanted in the peripheral (*left*) or central nervous system (*right*). Read-out implants (*top row*) control muscle activity or movement, whereas write-in implants (*bottom row*) lead to sensory perceptions.



ture with the prosthetic hand, and make the robot arm pick up and drop a piece of candy. Of late, he has even used the device, called BrainGate, to make precise copies of geometric figures.

Supplying Sensation

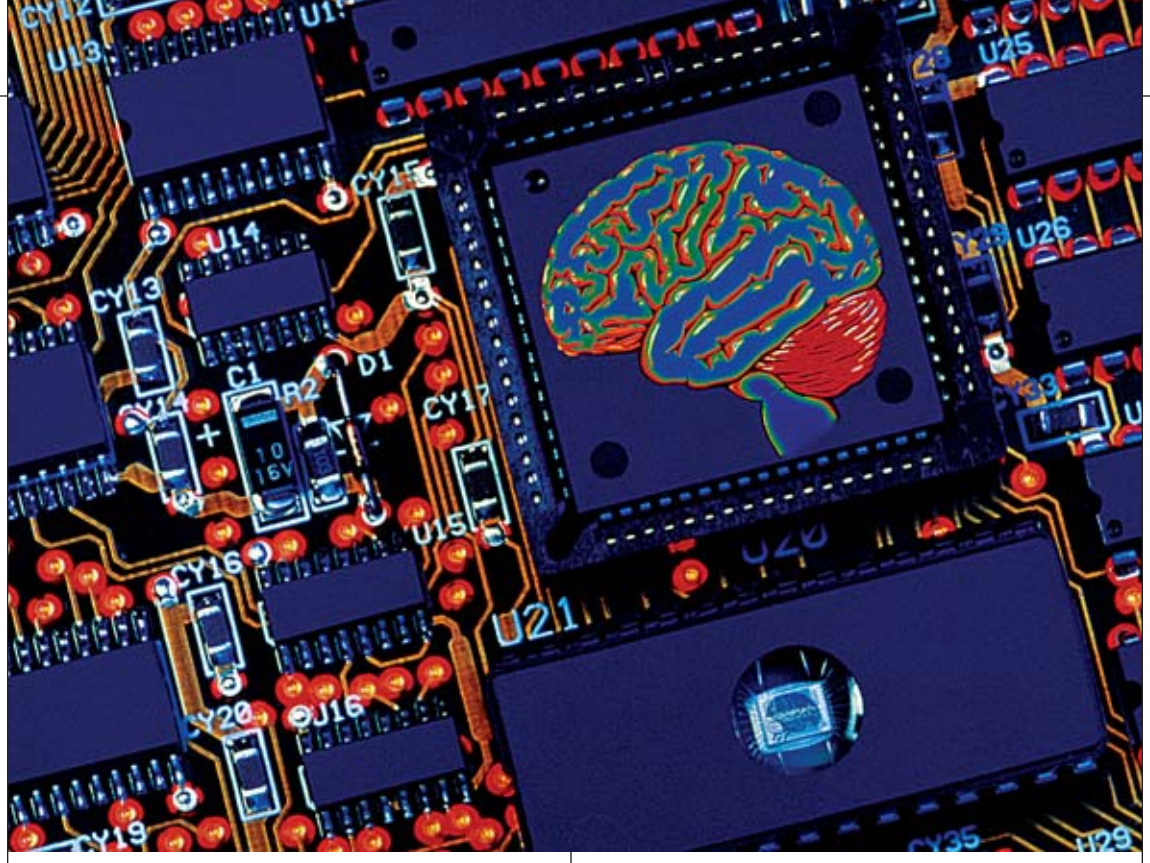
Whether in the body's periphery or the brain, such "read-out" prostheses detect and relay existing neuronal information—in these cases, motor information—rather than supplying their own signals and data. In contrast, "write-in" prosthetics feed information *into* the brain. Often they supply sensory input by transmitting signals from the environment to elicit sensations such as sight, sound and touch.

Write-in neuroprostheses are still limited to the periphery, that is, body regions outside the brain; some, for instance, are located in the sensory nerve tracts that conduct information to the brain from the eye or ear. Perhaps the most successful example of these is the cochlear implant. Sounds registered by a microphone are transformed into electrical impulses that directly stimulate the auditory nerve, which transmits signals from the ear to the brain. The implant thereby bypasses damaged parts of

(The Authors)

FRANK W. OHL is professor of neurobiology at the University of Magdeburg, and heads the BioFuture Research Group at the Leibniz Institute for Neurobiology in Germany. HENNING SCHEICH is director of the Leibniz Institute for Neurobiology.

GEHIRN & GEIST/SIGANIM



To be optimally effective, a sensory prosthesis implanted in the brain would need to integrate incoming sensory information with ongoing brain activity.

the ear itself, enabling some profoundly deaf people to recognize sounds in the environment and to hear and understand speech.

Another brain-input device currently in the testing stage could be the first successful attempt at creating artificial "eyes" for the blind. One such device, developed by researchers at Second Sight Medical Products in Sylmar, Calif., transmits images captured by a video camera to electrodes implanted in the retina at the back of the eye. The Second Sight implant has enabled blind subjects to perceive simple patterns and to distinguish among the light configurations emitted by different objects. In addition, bladder stimulators, such as the Finetech-Brindley system developed by Giles Brindley of the Medical Research Council in London, can help restore some bladder function to paralyzed people by supplying appropriate signals to the neurons that control the release of urine.

Many such peripheral devices, however, do not work in those whose eyes, ears or other organs have become disconnected from their brain through injury or disease. To overcome such problems, scientists have been working since the 1960s on write-in prostheses that could be implanted into the brain regions responsible for senses such as sight, hearing and touch. Thus, a brain implant for hearing might stimulate the auditory cortex, located behind the ears at the brain's surface, to elicit the perception of sound; to create sight, an implant might excite the visual cortex, located at the rear surface of the brain.

Such methods have provided only the most primitive sensations to date. Electrical probes in the auditory cortex, for instance, enable patients to hear little more than rustling or crackling sounds. And electrically stimulating the visual cortex can cause a patient to see spots of light called phosphenes. But no such device has produced apprehension of the edges and contours that define objects and scenes or the nuances of a conversation or song.

The technology used in such devices, which is not yet fully developed, is only partly to blame for these limitations. The problem is more fundamental. In contrast to peripheral nerves, the sensory cortex does not passively register sensory information the way a camera or audio recorder does. Rather perceptual brain regions are active on their own at all times, functioning, in all probability, to reinterpret incoming sensory data by matching them against related pieces of knowledge, an individual's past experiences and the brain's own expectations. That is, knowledge of the structure and meaning of words helps listeners interpret speech, whereas experience with the visual world helps people make sense of changes in a scene's lighting or perspective. To integrate such information into a perception, the sensory regions exchange data with other parts of the brain that govern higher thought processes. A sensory prosthesis implanted in the brain therefore has to integrate incoming information with ongoing brain activity.

OTTO ROGGE *Corbis*

Soundless Hearing

Along with physiologists and physicians, we are currently studying the fundamental principles of such a dialogue in Mongolian gerbils (*Meriones unguiculatus*), whose hearing is similar to that of humans at low frequencies. Scientists can also easily teach these gerbils behaviors that indicate what they are sensing. For example, they can be taught to jump from one compartment of a box over a hurdle and into a second compartment whenever they hear a specific cue, such as a low tone or a fast rhythm, and otherwise to stay put. In one experiment, we taught the gerbils to jump only on hearing two tones of ascending pitch. (They stood still if the higher note came first.) The rodents also learned a more complex sensory task: leaping only when they heard the same tone played repeatedly at shorter and shorter intervals.

After teaching the gerbils such tricks, we deafened them by experimentally damaging their inner ears. We then implanted prototypes of a two-electrode neuroprosthesis into their auditory cortex. One electrode stimulated a cortical region that processes high frequencies, and the other excited an area that represents low frequencies. With this device alone, these otherwise deaf gerbils could differentiate between high- and low-frequency tones and also detected changes in interval. Additionally, the animals could perceive combination patterns in which we altered both the location and the timing of the stimulation. The rodents learned to do these tasks just as well as gerbils that did not receive the brain implant but that heard the same sound patterns the normal way: through their ears.

Those experiments demonstrated that an auditory cortex implant can produce meaningful perception on its own. Our implant works better, however, if it is precisely synchronized with ongoing neural activity in the auditory cortex. The gerbils learned to tease apart the different sound patterns faster and more accurately when we stimulated that brain region during certain split-second phases of brain activity, as detected by an array of 18 recording electrodes, in comparison to other time points. This finding suggests that the prosthesis is dependent on information exchange with the stimulated regions of the cortex. To automate this synchrony, a write-in cerebral prosthesis would also have to read and interpret existing auditory brain signals and use them to calibrate its own activity.

These promising early results prompt the question: Do brain prostheses pose ethical or moral dilemmas that, say, artificial hands or eyes do not? When scientists or doctors decide to tinker directly with the brain, a person may feel that he or she is being altered in a profound, even spiritual way. In principle, a sensory prosthesis in the brain does fundamentally transform a person, because such a device alters an individual's perception of the world. On the other hand, so do many ordinary events of daily life. People are constantly experiencing new things, learning and changing. In doing so, everybody's sense of self is continually evolving.

And yet the deeper scientists penetrate into the mind, the greater the risk of crossing a line between replacing biological hardware and altering an individual's sense of self. As interactive neuroprostheses mature, their developers will need to consider the social and ethical ramifications of their advances. If they manage to do so, we forecast a bright future for synthetic supplements to the brain. M

Do brain prostheses pose ethical or moral dilemmas that, say, artificial hands or eyes do not?

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For half a century, lithium salts have saved thousands from the potentially lethal grip of bipolar disorder. Surprising new findings now hint that these salts may also offer hope as treatments for neurological ailments from Alzheimer's disease to stroke

Lithium's Healing Power

By Jochen Paulus

Ever since her senior year in high school, Kay Redfield Jamison has spent days and even weeks exploding with energy. She would stay up all night, sometimes for weeks in a row, feeling euphoric and productive. She would become lively, extroverted and impulsive. She would make bizarre purchases—a stuffed fox one day and a dozen snakebite kits the next.

Then, suddenly, it would end, and Jamison would descend into darkness. She would lose interest in work, friends and hobbies. She would feel listless, drained and totally alone. During these periods, thoughts of death and decay plagued her. More than once, she flirted with suicide. "From the time I woke up in the morning until the time I went to bed at night, I was unbearably miserable and seemingly incapable of any kind of joy," she wrote in her memoir, *An Unquiet Mind* (Alfred A. Knopf, 1995).

GETTY IMAGES

Two to 3 percent of Americans **swing wildly** from manic phases to depressed periods.

Kay Redfield Jamison, who has long suffered from bipolar disorder, now studies her own ailment as a professor at the Johns Hopkins School of Medicine.

Jamison, 60, has long fought the extreme mood swings of bipolar disorder, also known as manic depression. Two to 3 percent of American adults share her torment. Like Jamison, they swing wildly from manic phases, in which they are ecstatic and energetic, to depressive periods, in which they are sad, dejected and hardly able to function. These radical fluctuations in behavior and emotion can ruin marriages, damage job or school performance, and often lead to suicide.

On her doctor's advice, in 1974, Jamison began taking lithium salt, a so-called mood stabilizer. At first, she took her medicine sporadically. She disliked its troublesome side effects, which ranged from limb trembling and slurred speech to nausea, but mostly she missed the intoxicating highs of her former self. She finally decided to stick with the treatment after she attempted suicide, and her moods largely became stable. She is now a psychiatry professor at the Johns Hopkins School of Medicine. Her specialty: the disorder that plagues her.

Like Jamison, hundreds of thousands of people owe their mental stability to the alkali metal lithium. Patients take salts of this element, such as lithium carbonate, lithium sulfate or lithium citrate, that break down into ions in the body, including the positively charged lithium ion Li+, which is thought to be the active ingredient. In about two thirds of patients the treatment successfully suppresses their drastic emotional shifts.

The drug is unique in its ability to dramatically lower the suicide rate in patients with manic depression and other mood disorders. Up to 15 percent of patients with the disorder eventually succeed in committing suicide. Lithium can prevent about 60 percent of such tragedies, according to a 2005 report by John Geddes of the University of Oxford and his colleagues, in which the researchers analyzed the results of dozens of studies of the drug's efficacy.

Lithium may be more than just a wonder drug for many bipolar patients. New studies of its actions in the brain suggest that its job may not be limited to changing the way nerve cells respond to stimuli. It may also promote brain cell survival. If these preliminary findings hold up, doctors may one day be prescribing the drug for a variety of neurological disorders.

Salty Sedative

Lithium's powers as a psychoactive drug were first discovered in the 1940s, when Australian psychiatrist John Cade wondered whether the disorder then known as mania might result from intoxication by normal body products, such as those in urine. To test this curious idea, he injected guinea pigs with lithium urate, the most soluble of the simple urate salts. He found that the salt was not toxic but instead seemed to make the animals calmer. When Cade tested lithium urate on 10 manic patients, all of them became similarly more sedate.

Cade's report, which appeared in the *Medical Journal of Australia* in 1949, attracted little notice until Danish researcher Mogens Schou chanced on it in 1952. Seeking more solid support for Cade's hypothesis that lithium could pacify people with mania, Schou and his colleagues at Aarhus University conducted the first controlled studies of a psychotropic drug anywhere. They treated a group of manic patients, some of them with lithium and others with a placebo, and found that lithium was indeed more effective than placebo in treating the disorder, a result they published in 1954.

The medical community did not immediately embrace lithium or Schou's work. As late as the 1960s, many scientists and doctors attacked Schou and his findings in the scientific literature. The new drug had a particularly difficult time in the U.S, where lithium chloride had been used during the 1940s as a salt substitute, and toxic doses had killed several heart patients. Its use was banned in this country until Ronald Fieve, a psychopharmacologist at the Columbia College of Physicians and Surgeons, conducted a series of rigorous studies of lithium during the mid- to late 1960s. Fieve's work finally led to lithium's approval as a medication in the U.S. in 1970.

Boosting Brain Matter

For many years after lithium's powers were recognized, neuroscientists still had little notion of how the drug dampened the passions of patients with bipolar disorder. Many assumed that

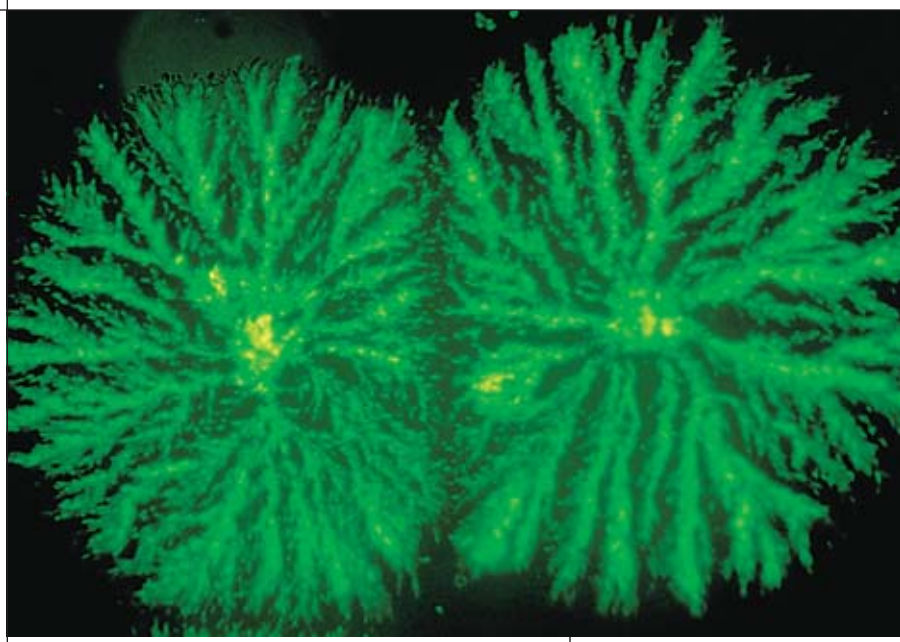
JOHNS HOPKINS SCHOOL OF MEDICINE

it somehow altered levels of neurotransmitters (chemical messengers) in the brain and thereby corrected a chemical imbalance that was presumed to underlie the mood disorder. Although that theory is still thought to be partially correct, it does not fully explain what lithium does to neurons. For one, despite the fact that lithium alters neurotransmitter concentrations quickly—within hours—it takes a week or longer to relieve symptoms of depression.

In the 1980s many researchers championed the idea that lithium works by inhibiting the production of the sugar inositol, which forms the backbone of a number of important signaling molecules within a cell. Lithium reduces the concentration of inositol in cultured cells and in the rodent brain. Such a deficit could, for example, alter the way a neuron responds to chemical signals from another neuron. It is unclear, however, whether inositol levels are too high in patients with bipolar disorder, and no one has been able to prove that lithium's effects are a result of reductions in inositol.

Over the past several years, researchers have begun to chase a different set of molecular targets for lithium, those that control not only neuronal signaling but also cell survival. For example, lithium helps to block the potentially lethal actions of the excitatory neurotransmitter glutamate; it also suppresses an enzyme called glycogen synthase kinase-3 (GSK-3), which can set in motion events that cause cell death [*see box on next page*]. In doing so, lithium may work to boost the number of neurons in the brain.

Relative to normal people, patients with bipolar disorder have notably less gray matter, which primarily consists of neuron cell bodies. Depending on the area of the brain, the shortfall is as much as 30 percent, either because nerve cells have died or because they have failed to develop in the first place. Lithium does seem to increase neuronal numbers to some extent. A team of researchers led by psychiatrist Husseini Manji, now at the National Institute of Mental Health (NIMH), used brain imaging to measure the volume of gray matter in patients with bipolar disorder before and after four weeks of treatment with lithium. They reported in 2000 that overall gray matter volume had increased as much as 8 percent after lithium treatment. The effect may be more pronounced in particular brain regions. In mice, Manji and his colleagues reported that the drug increased the number of neurons by 25 percent in a part of the hippocampus, a region involved in memory.



RAPHO AGENCE DE PRESSE/PHOTOTAKE

Lithium salt, shown here in crystal form, may one day help treat patients afflicted with Alzheimer's and Huntington's diseases.

Salve for Sore Minds?

Such studies have led researchers to wonder whether lithium might be effective in treating classic neurodegenerative diseases, such as Alzheimer's or Huntington's, and other problems that lead to the death of neurons, such as stroke. So far a small number of animal and early-stage human studies support this notion.

For example, a research team led by Yuan Su at Lilly Research Laboratories in Indianapolis discovered that lithium abolished or reduced certain hallmarks of Alzheimer's in the brains of mice genetically prone to developing the disorder. Lithium is thought to thwart Alzheimer's disease processes, such as the accumulation of plaque in the brain, in part by inhibiting GSK-3.

In addition, preliminary data suggest that people with bipolar disorder who have been taking lithium for a long period may be less likely to acquire Alzheimer's than people who have not been taking the drug. In a 2006 study of the medical records of 1,423 elderly outpatients who visited a clinic at Oita University Faculty of Medicine in Japan, the patients who had received lithium treatment had higher scores on a test of mental function than people of the same age and sex who had never been prescribed lithium. But a 2005 study by Nick Dunn of the University of Southampton in England and his colleagues points in the opposite direction. Dunn's team found that patients who take lithium actually stand a great-

(The Author)

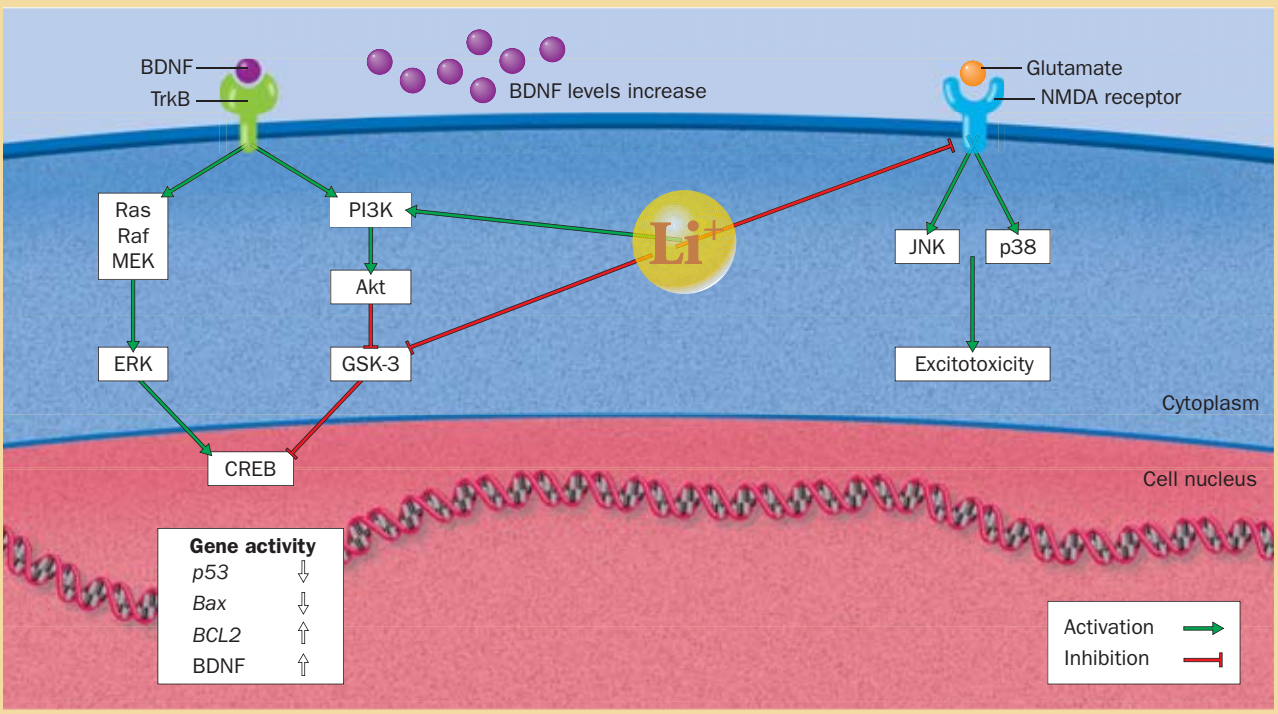
JOCHEN PAULUS is a freelance journalist in Landau, Germany, and has been following developments in lithium therapy for many years.

Lithium at Work

Lithium acts on several different molecular pathways inside nerve cells that influence their survival. The enzyme glycogen synthase kinase-3 (GSK-3), whose activities can lead to cell death, is a prime target of the drug. Lithium inhibits GSK-3 directly and also indirectly, by activating an enzyme called phosphoinositide 3-kinase (PI3K), which suppresses GSK-3 via the enzyme protein kinase B (Akt).

GSK-3 inhibits a protein in the cell nucleus called cyclic AMP response element binding protein, or CREB, which otherwise shores up cell survival by regulating the activity of various genes. CREB inhibits the reading of potentially destructive genes, such as those for *p53* and *Bax,* which mediate the toxic effects of the neurotransmitter glutamate. In addition, CREB boosts the expression of genes such as *B cell lymphoma 2* (*BCL2*), which helps neurons regenerate after damage and can halt apoptosis, the process of cell suicide. By interfering with GSK-3 activity, lithium prevents the enzyme from inhibiting these important CREB functions.

Lithium's actions also include raising levels of brain-derived neurotrophic factor (BDNF). This growth factor sets in motion a parallel pathway that activates CREB and thus enhances cell survival. Finally, lithium works at the NMDA receptor, the receptor for the excitatory neurotransmitter glutamate. It binds to the receptor and changes its structure, thereby preventing glutamate from fatally overstimulating the cell. *—J.P.*



GEHIRN & GEIST/ART FOR SCIENCE; SOURCE: "LITHIUM: POTENTIAL THERAPEUTICS AGAINST ACUTE BRAIN INJURIES AND CHRONIC NEURODEGENERATIVE DISEASES," BY AKIHIKO WADA ET AL., IN *JOURNAL OF PHARMACOLOGICAL SCIENCES*, VOL. 99, NO. 4; 2005

er chance than others of developing dementia.

Such contradictory results underscore the early stage of the field. "These are amazing findings," says psychiatry researcher Dietrich van Calker of the University Medical Center in Freiburg, Germany. But van Calker warns that taking lithium to prevent symptoms of Alzheimer's would be going "overboard."

At least one study in rats suggests lithium might also ameliorate the devastating symptoms of Huntington's, in which uncontrollable spasmodic motions are caused by cell death in the striate body, an area of the brain involved in the planning and control of movement. Later, further neuronal death degrades higher thought and memory functions. Neurobiologist De-Maw Chuang and his colleagues at the NIMH simulated early Huntington's in rats by infusing the rodent striate body with quinolinic acid, which triggers neuronal death. In 2004 Chuang's team reported that rats that received lithium before and soon after the acid treatment lost significantly fewer neurons than rats that received only the acid. Lithium blocked cell suicide signals and also seemed to spur the proliferation of neurons.

Lithium may prevent the **death of brain cells** after a stroke or from radiation treatment for tumors.

Defying Death

If lithium can attenuate cell death, it might also help reduce the damage from stroke, in which brain cells succumb after arteries feeding the brain rupture or become blocked. As the blood supply diminishes, the cells become starved of oxygen. This starvation, in turn, is thought to induce the excessive release of glutamate, thereby overstimulating certain receptors on other nerve cells and unleashing a cascade of events that culminates in cell death. Lithium may interfere with this fatal process, in part by binding to and inactivating NMDA, the receptor that ordinarily responds to glutamate.

Indeed, rat studies suggest that the drug may considerably reduce brain damage after a stroke. Chuang's team showed that lithium treatment reduced both brain damage and neurological problems in rats that had suffered experimental strokes. Lithium was effective if the rats received it within three hours after the brain injury, the researchers reported in 2003. Thus, the agent might work as an acute treatment for stroke as well as a way to limit the damage in patients at risk for having a stroke.

Through similar means, lithium might also lower the risk of brain damage from radiation treatment for brain tumors if taken before the treatment. Radiation can damage nerve cells, particularly those in the brain's hippocampus. In 2006 oncologist Dennis Hallahan of Vanderbilt University and his colleagues reported that giving lithium to rats before radiation exposure protected the rodents against neuron death in the hippocampus and preserved the animals' performance on mental function tests, such as navigating a maze, relative to irradiated rats that did not receive lithium.

Other surprising uses for lithium include the prevention of schizophrenia. Recent research suggests that schizophrenia may stem from the loss of certain brain cells and the failure of others to grow and develop—a process that lithium might conceivably counteract. Data to support that hypothesis come from psychiatrist Gregor Berger of the University of Melbourne in Australia. Berger and his colleagues treated 30 young adults at high genetic risk for schizophrenia or other psychoses with lithium for a year or longer. Statistically, a quarter of the test subjects should have begun to show signs of schizophrenia by now, but none of Berger's patients has exhibited any symptoms of the illness so far, hinting that lithium may have a prophylactic effect.

Still, lithium's promise in these diverse disorders must be borne out in further studies—ultimately, large ones done in humans—before anyone can consider it therapy for anything but bipolar disorder. "That's still way in the future," warns psychiatry researcher Michael Bauer, who studies mood disorders at Charité Medical School in Berlin. Not only are the findings to date highly preliminary in most cases, but lithium can also be toxic. For some patients, the therapeutic dose of the substance is dangerously close to the toxic dose. Doctors must closely monitor blood levels of lithium in their patients to minimize side effects, such as hand tremors, dry mouth, weight gain, blurred vision, confusion and seizures.

But perhaps lithium's largest liability is its very identity. As a chemical element, it cannot be patented or reap profits for pharmaceutical firms. Thus, drug company executives are disinclined to spend millions for the clinical trials needed to prove its efficacy in various neurological disorders. "[Drug companies] want to sell their own substances," Bauer points out, and industry scientists are trying to develop patentable mimics of the metal. In some ways, that seems like a pricey redundancy, because the natural material works so well. Jamison is proof of that. Without this medication, she penned in *An Unquiet Mind,* "I would be constantly beholden to the crushing movements of a mental sea; I would, unquestionably, be dead or insane." M

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CHRIS HARTLOVE *Getty Images*

A Personal Obsession

What drives stalkers to pursue their victims?

By Isabel Wondrak and Jens Hoffmann

One day recently Helene K., a 50-year-old occupational therapist, received a call at home from a former patient. It took her several minutes to remember the man, who had been discharged from her clinic more than a year earlier. He said he would like to see her again, but Helene firmly rejected the idea: she wanted no further contact with him.

Then came more phone calls from the man, as well as letters declaring his love for her. One morning Helene opened her front door and saw the man standing there, suitcase in hand; he had resigned from his job and wanted to move in with her. Helene demanded that he leave her alone, but instead he began following her everywhere.

When Helene changed her phone number and got a restraining order, her tormentor responded with threatening letters. Despite three fines imposed by the court—the last one for more than $6,000—the man continued harassing Helene and her neighbors as well.

Women are the primary victims of stalking, and men are the main perpetrators.

Not Just Celebrities

Society's familiarity with stalking stems mainly from tragic and highly publicized "celebrity stalking" incidents over the past three decades: John Lennon gunned down outside his New York City home by Mark David Chapman in 1980; actress Rebecca Schaeffer fatally shot by obsessed fan Robert Bardo in 1989; tennis star Monica Seles stabbed during a Hamburg tennis match by a deranged Steffi Graf fan in 1993. More recent (and nonviolent) celebrity stalker cases have involved Madonna, Brad Pitt, David Letterman, Steven Spielberg, Linda Ronstadt and Ashley Judd.

Unfortunately, the publicity surrounding celebrity stalking has tended to distract us from its surprisingly high prevalence in the general population. For every Linda Ronstadt plagued by a stalker, thousands of Helenes are similarly traumatized.

In 1998 the National Institute of Justice and the Centers for Disease Control and Prevention published *Stalking in America,* the first ever (and so far only) national survey on stalking and its impact, based on a representative telephone survey of 8,000 U.S. women and 8,000 U.S. men, 18 years and older. (The survey defined stalking as "a course of conduct directed at a specific person that involves repeated visual or physical proximity, nonconsensual communication, or verbal, written or implied threats, or a combination thereof, that would cause a reasonable person fear.")

Among the study's highlights:

- Women—by four to one—are the primary victims of stalkers.
- Men are the primary perpetrators of stalking, accounting for 94 percent of the stalkers identified by female victims and 60 percent of the stalkers identified by male victims.
- In the U.S., 8 percent of women and 2 percent of men have been stalked at some time in their life. Based on U.S. census population estimates, this means that 9.4 million women and 2.3 million men have been stalked.
- Most victims know their stalker. Only 23 percent of female stalking victims and 36 percent of male victims were stalked by strangers.
- Women tend to be stalked by intimate partners (defined as current or former spouses, cohabitants, boyfriends or girlfriends). Overall, 59 percent of female victims were stalked by an intimate partner, whereas 30 percent of male victims were stalked by an intimate partner.
- Nearly one fifth of all victims move to new locations to escape their stalkers.
- About two thirds of all stalking cases last a year or less, about a quarter of cases last two to five years, and about a tenth last more than five years.

The Mind of the Stalker

What does "stalking" mean? The term comes from the word describing the phase of hunting prior to the kill, in which a predator tracks and approaches its prey, boxing in the quarry and never letting it out of sight. Stalkers not only obsessively monitor their targets but repeatedly accost them as well—through phone calls, e-mails, letters or encounters on the street. Some stalkers also send gifts or more frightening fare, such as a photo collage with the victim's face replaced by a skull. Stalkers may also order merchandise in their victims' name or start vicious rumors about them.

Bettina M., age 28, had a boyfriend who was extremely controlling and so jealous that he discouraged her from talking to other men. Although Bettina broke up with him after three months, they maintained contact because they worked in the same office. He proceeded to hack into her e-mail account and read her incoming and outgoing messages.

He also assailed her with instant messages—some pleasant, some pleading, some threatening. He later logged on to an online forum that she belonged to—and announced to other subscribers that Bettina had committed suicide. When Bettina eventually found a new boyfriend, her stalker followed the couple around and later bombarded them with instant messages describing what he had seen.

What drives people to such behavior? Studies show that stalkers typically have experienced failures in life and lack a current intimate partner. They also tend to be unemployed. Not uncommonly, stalkers suffer from mental illness, including major depression and a variety of personality disorders—yet psychosis tends to be con-

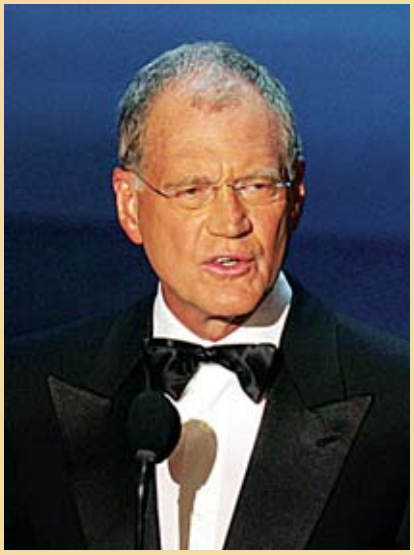
Star Struck

So-called celebrity stalkers are more likely than other types to be psychotic. They take refuge in a delusion in which they are happily united with a famous person. Most star stalkers are "identity vampires," yearning that their proximity to fame will fill the deficits they perceive in their own personas. They also hope their intrusions will elicit a reaction from the celebrity—but if not, they will increase the intensity of their attention-getting efforts.

In 2001 the Darmstadt Workshop for Forensic Psychology carried out the first study of celebrity stalking in the German-speaking world, involving interviews with 53 famous people from entertainment and the media. Some 80 percent of them had been targeted at least once—a rate about eight times that of the general public. Neither age nor sex influenced the probability that a celebrity would be stalked. Instead the decisive factor was how often the person had appeared on talk shows or in the press.

The Darmstadt study showed that celebrities who reveal their private lives to the public make it easier for stalkers to get attached to them—increasing the intensity and therefore the risk of the stalking endeavor. Fortunately, celebrity stalkers rarely used violence against their targets: as noted, they tend to be psychotic—and studies show that psychotic stalkers tend to be less violent than stalkers with a less severe psychological disorder.

—*I.W.* and *J.H.*



John Lennon's murder was unusual in the annals of celebrity stalking. More typical was the experience of David Letterman, who was hassled by a nonviolent stalker.

GETTY IMAGES (*left*); ROBERT GALBRAITH *Reuters/Corbis* (*right*)

fined mainly to celebrity stalkers [*see box above*]. Stalkers act after being influenced by emotions that may include longing, despair, blame, obsessive love, and anger or vengefulness at being rejected.

Between 2002 and 2005 our research team at the Technical University of Darmstadt carried out the first German study of stalkers. We interviewed some 100 currently active stalkers who contacted us anonymously after we placed an ad on the Internet, and we came to an overriding conclusion: our subjects had difficulty accepting reality.

Despite their lack of success in winning over or winning back their prey, four out of five stalkers told us that they planned to continue their stalking behavior. Why? The answer given most often was that they felt they were "destined" to be with their victims. One third of our sample said that stalking was their way of breaking down the resistance of those who—in their heart of hearts—surely wanted to be with them as well. Another third said they had an obligation to take care of the ones they loved. Clearly, no matter how often a target rejects a stalker's approaches, the stalker won't take no for an answer.

Our survey also offered insight into the emotional lives of stalkers, who are often unhappy. More than 60 percent said they suffered from emotional problems, such as depression. A third were being treated by a physician or psychologist for anxiety. And nearly 40 percent of the stalkers we surveyed admitted to being repeat offenders.

The Traumatized Victims

Between 2002 and 2004 we also interviewed some 550 stalking victims to learn how their ordeal had affected them. Unlike people who experience a single traumatic event, stalking victims

(The Authors)

ISABEL WONDRAK and JENS HOFFMANN are psychologists who work at the department of forensic psychology of the Technical University of Darmstadt in Germany. They also head the Institute for Psychology and Security in Aschaffenburg.

typically must deal with their painful situation many times—sometimes every day over the course of years: whenever the phone rings, a victim might immediately think of the stalker. A "normal" life is usually out of the question in such an atmosphere of anxiety and helplessness.

Our survey of stalking victims found that the average duration of a stalking case was 28 months, but in one case it had lasted for 30 years. Victims typically felt threatened in three or four places they visited regularly—their favorite bar, their neighborhood supermarket or their health club, for example. But most often, and most chillingly, the stalking occurred at home.

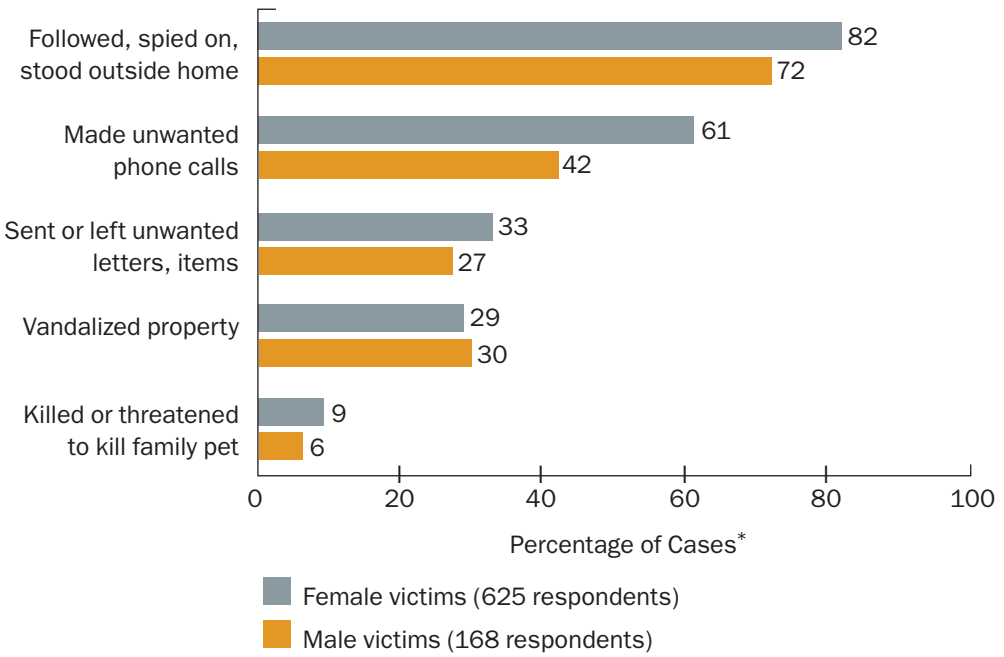
Many victims reacted by barricading themselves against intrusion of any kind—keeping their curtains closed, installing home security systems, procuring unlisted phone numbers they would give to just a few people. Not surprisingly, living in a state of siege dramatically affected these people's social life. Getting together with family and friends was difficult, and problems with partners were common. In addition, one in five stalking victims ended up moving away, and one in 10 resigned from his or her job.

Over time, our survey found, most stalking victims are psychologically traumatized by their ordeal. Many were ashamed of being stalked and even blamed themselves for their predicament. Two thirds suffered from emotional problems, including depression, anxiety, panic attacks, difficulty concentrating, and eating and sleeping disorders. In addition, the stress from being stalked had typically caused victims to become more irritable, angry and aggressive than they had been before the stalking began. One in four victims said they had considered suicide or had made an actual suicide attempt. And in most cases, the emotional trauma of being stalked persisted even after the stalking finally ended. Our research has shown that stalkers are able to exert tremendous control over their victims' life even though physical abuse typically does not occur. In one of five cases, however, we found that the stalker does resort to violence in the form of beatings, armed assaults or even attempted murder.

Intimate Past, Violent Future

The *Stalking in America* survey and other studies of stalkers have all reached the same sobering conclusion about violence in stalking: it is most likely when the stalker and victim have had an intimate relationship. Recently researcher and forensic psychologist Kris Mohandie of Operational Consulting International and his col-

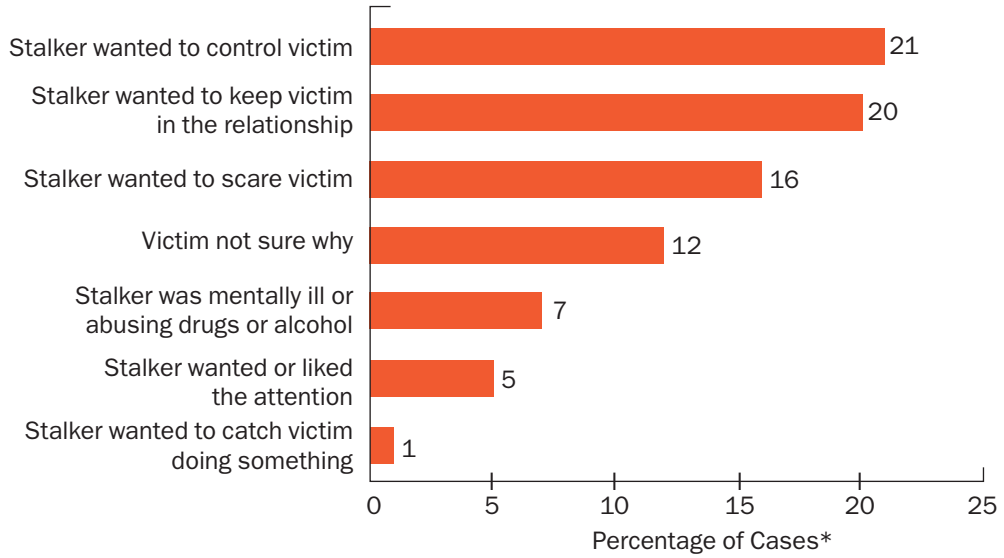
Common Stalking Activities



*Percentages exceed 100 percent because question had multiple responses

SOURCE FOR BOTH GRAPHS: *STALKING IN AMERICA: FINDINGS FROM THE NATIONAL VIOLENCE AGAINST WOMEN SURVEY*, BY PATRICIA TJADEN AND NANCY THOENNES. NATIONAL INSTITUTE OF JUSTICE AND CENTERS FOR DISEASE CONTROL AND PREVENTION, 1998

Victims' Perceptions of Why They Were Stalked



*624 male and female victims in total

leagues analyzed a nonrandom sample of 1,005 North American stalking cases gathered from prosecutorial agencies, a Canadian police agency and other sources.

Their findings, published last year in the *Journal of Forensic Sciences*, showed that among four categories of stalking studied (that of an acquaintance, a celebrity, a stranger or an intimate partner), personal violence occurred in more than 50 percent of cases in which stalker and victim had been intimate—by far the highest incidence in any category. But stalking of any kind clearly heightens risk of harm: whereas homicide in this study's total sample was very rare (0.5 percent), stalking victims nonetheless faced at least 50 times the homicide risk of the general population.

What should people do if they are being stalked? How *not* to react may be more important for bringing the stalking to an end.

J. Reid Meloy, associate clinical professor of psychiatry at the University of California, San Diego, has conducted numerous studies of stalkers. "The worst response for a stalking victim is to initiate direct contact with the threatening person," wrote Meloy in 2002 in the *Journal of the American Academy of Psychiatry and the Law*. Regardless of the message, he notes that "the act itself becomes an intermittent positive reinforcement and causes a significant increase in pursuit behavior." He and his colleagues found that among female stalkers, stalking increased in intensity in 68 percent of cases in which victims initiated contact after stalking began.

Stalking is a serious societal problem that can result in violence, particularly in situations where stalker and victim have been intimately involved. Even in the absence of violence, stalking can be emotionally traumatic for victims as well as their families and neighbors. Those who feel they are being stalked should promptly ask law enforcement or the courts to intervene.

In the years since California became the first state to criminalize stalking in 1990, all 50 states, the District of Columbia and the federal government have followed suit. By aggressively confronting stalkers, the police can deter some of them early in their stalking efforts. Similarly, obtaining a court order against a stalker can serve as a deterrent. For assistance and advice, victims can also call the National Center for Victims of Crime at 800-FYI-CALL. M

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Autism: An Epidemic?

A closer look at the statistics suggests something more than a simple rise in incidence

BY SCOTT O. LILIENFELD AND HAL ARKOWITZ

IF THE FIGURE of "one in 166" has a familiar ring, perhaps that's because you recently heard it on a television commercial or read it in a magazine. According to widely publicized estimates, one in 166 is now the proportion of children who suffer from autism. This proportion is astonishingly high compared with the figure of one in 2,500 that autism researchers had accepted for decades. Across a mere 10-year period—1993 to 2003—statistics from the U.S. Department of Education revealed a 657 percent increase in the nationwide rate of autism.

Not surprisingly, these bewildering increases have led many researchers and educators to refer to an autism "epidemic." Representative Dan Burton of Indiana also declared in 2001 that "we have an epidemic on our hands." But what's really going on?

Before we explore this question, a bit of background is in order. Autism is a severe disorder that first appears in infancy. Individuals with autism are characterized by problems in language, social bonding and imagination. All suffer from serious communication deficits, and some are mute. They do not establish close relationships with others, preferring to remain in their own mental worlds. They engage in highly stereotyped and repetitive activities, exhibiting a marked aversion to change. About two thirds of autistic individuals are mentally retarded. For reasons that are unknown, most are male.

The causes of autism remain enigmatic, although studies of twins suggest that genetic factors play a prominent role. Still, genetic influences alone cannot account for such a rapid and astronomical rise in a disorder's prevalence over a matter of just a few years.

As a consequence, investigators have turned to environmental factors for potential explanations. The causal agents proposed include antibiotics, viruses, allergies, enhanced opportunities for parents with mild autistic traits to meet and mate, and, in one recent study conducted by Cornell University researchers, elevated rates of television viewing in infants. Few of these explanations have been investigated systematically, and all remain speculative.

Problem Shots?

Yet one environmental culprit has received the lion's share of attention: vaccines. At first blush, vaccines would seem to make a plausible candidate for the source of the epidemic. The debilitating symptoms of autism typically become apparent shortly after age two, not long after infants have received vaccinations for a host of diseases. Indeed, many parents claim that their children developed autism shortly after receiving inoculations, either following a vaccine series for mumps, measles and rubella (German measles)—the so-called MMR vaccine—or following vaccines containing thimerosal, a preservative containing mercury.

Much of the hype surrounding a vaccine-autism link was fueled by a widely covered investigation of 12 children published in 1998 by British gastroenterologist Andrew Wakefield and his colleagues. The study revealed that symptoms of autism emerged shortly after the children received the MMR vaccine. (Ten of the 13 authors have since published a retraction of the article's conclusions.) Public interest in the vaccine-autism link was further stoked by the provocatively titled book *Evidence of Harm* (St. Martin's Press, 2005), written by investigative journalist David Kirby, which was featured in an extended segment on NBC's *Meet the Press*.

Yet recently published research has not been kind to the much ballyhooed vaccine-autism link. The results of

COURTESY OF SCOTT O. LILIENFELD (*top*); COURTESY OF HAL ARKOWITZ (*bottom*); CAROL AND MIKE WERNER *Phototake* (*child in cube*)

Recently published research has not been kind to the much ballyhooed **vaccine-autism link**.

several large American, European and Japanese studies demonstrate that although the rate of MMR vaccinations has remained constant or declined, the rate of autism diagnoses has soared. In addition, after the Danish government stopped administering thimerosal-bearing vaccines, the rates of autism continued to rise. These studies and others, summarized by the Institute of Medicine, suggest there is little evidence that vaccines cause autism. It is possible that vaccines trigger autism in a small subset of children, but if so that subset has yet to be identified.

Changing Criteria

Making matters more confusing, ample reason exists to question the very existence of the autism epidemic. Vaccines may be what scientists call an "explanation in search of a phenomenon." As University of Wisconsin–Madison psychologists Morton Ann Gernsbacher and H. Hill Goldsmith and University of Montreal researcher Michelle Dawson noted in a 2005 review, there is an often overlooked alternative explanation for the epidemic: changes in diagnostic practices. Over time the criteria for a diagnosis of autism have loosened, resulting in the labeling of substantially more mildly afflicted individuals as autistic.

Indeed, the 1980 version of the American Psychiatric Association's diagnostic manual (DSM-III) required individuals to meet six of six criteria for an autism diagnosis. In contrast, the 1994 version (DSM-IV), which is currently in use, requires individuals to meet any eight of 16 criteria. Moreover, whereas DSM-III contained only two diagnoses relevant to autism, the DSM-IV contains five such diagnoses, including Asperger's syndrome, which most researchers regard as a high-functioning variant of autism.

Legal changes may also be playing a significant role. As Gernsbacher and her colleagues noted, an amended version of the Individuals with Disabilities Education Act (IDEA), passed by Congress in 1991, required school districts to provide precise counts of children with disabilities. IDEA resulted in sharp surges in the reported numbers of children with autism. Nevertheless, these numbers are not based on careful diagnoses of autism or on representative samples of the population. As a consequence, researchers who rely on "administrative-based estimates," which come from government data submitted by schools, will arrive at misleading conclusions about autism's prevalence. They must instead rely on "population-based estimates," which are developed from statistically reliable and representative surveys of autism's occurrence in the general population.

Further contributing to the reported increase may be the "Rain Man Effect," the public's increased familiarity with autism following the 1988 Academy Award–winning film starring Dustin Hoffman and Tom Cruise.

Numbers Analyzed

Two recent studies buttress assertions that the autism epidemic may be more illusory than real. First, in 2005 psychiatrist Suniti Chakrabarti of the Child Development Center in Stafford, England, and psychiatrist Eric Fombonne of McGill University conducted an investigation that used rigorous population-based estimates to track the prevalence of autism diagnoses from 1992 to 1998 in a sample of more than 10,000 children in the same area of England. They found no support for a change in prevalence, suggesting that when researchers maintain the same criteria for autism, the rates of diagnosis do not change over time.

Second, a 2006 article by University of Wisconsin–Madison psychologist Paul Shattuck cited "diagnostic substitution": as the rates of the autism diagnosis increased from 1994 to 2003, the rates of diagnoses of mental retardation and learning disabilities decreased. This finding raises the possibility that the overall "pool" of children with autismlike features has remained constant but that the specific diagnoses within this pool have swapped places.

It is still too early to exclude the possibility that autism's prevalence is growing, but it is unlikely that it is growing at anywhere near the rate many have suggested. As the late Eastern Michigan University sociologist Marcello Truzzi once said, extraordinary claims require extraordinary proof. The claim of an enormous epidemic of autism diagnoses is indeed extraordinary. Yet the evidence in support of this claim leaves much to be desired. **M**

SCOTT O. LILIENFELD and HAL ARKOWITZ serve on the board of advisers for *Scientific American Mind*. Lilienfeld is a psychology professor at Emory University, and Arkowitz is a psychology professor at the University of Arizona. Send suggestions for column topics to editors@sciammind.com

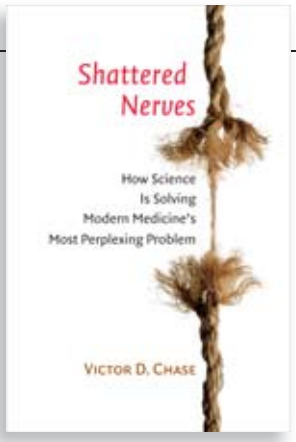
(Further Reading)

- **Separating Fact from Fiction in the Etiology and Treatment of Autism: A Scientific Review of the Evidence.** J. D. Herbert, I. R. Sharp and B. A. Gaudiano in *Scientific Review of Mental Health Practice,* Vol. 1, No. 1, pages 23–43; Spring–Summer 2002.
- **The Prevalence of Autism.** E. Fombonne in *Journal of the American Medical Association,* Vol. 289, No. 1, pages 87–89; 2003.
- **Immunization Safety Review: Vaccines and Autism.** Immunization Safety Review Committee. Board of Health Promotion and Disease Prevention, Institute of Medicine. National Academy Press, 2004.
- **Three Reasons Not to Believe in an Autism Epidemic.** M. A. Gernsbacher, M. Dawson and H. H. Goldsmith in *Current Directions in Psychological Science,* Vol. 14, pages 55–58; 2005.

Shocking Science

Shattered Nerves: How Science Is Solving Modern Medicine's Most Perplexing Problem

by Victor D. Chase. Johns Hopkins University Press, 2006 ($27.50)



Almost from the time electricity was discovered, scientists suspected it was involved in human and animal motion. They used electricity to make frogs' legs jump and, less successfully, to try to reanimate the dead.

Today modern science can use a judicious jolt of electricity to restart a stopped heart under the right circumstances. Much more difficult has been the attempt to use implanted electrodes to restore function to body parts affected by nerve damage.

Science and technology writer Victor D. Chase tells the story of the effort to create these "neural prostheses," providing an exhaustive look at the researchers and the technological innovations that have returned hearing and movement to nerve-damaged patients. Nerve impulses are electrochemical, and an obvious solution to damage would be to bypass the injured site and stimulate the nerves directly by running current through an electrode.

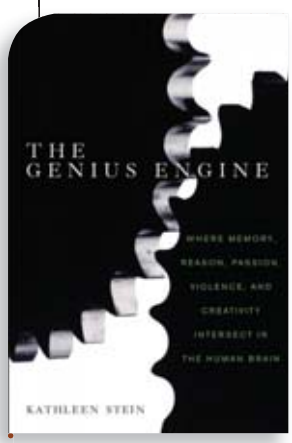
But what is simple in principle is hard in practice. Even the smallest electrodes are blunt instruments compared with the nerves they are trying to stimulate. Researchers would like to excite each nerve individually and to develop a controller as finely tuned as the human brain. What they often settle for are a few electrodes affecting a lot of nerves with relatively unsophisticated controllers.

Yet there have been successes. Probably the most familiar story is that of the cochlear implant, which activates the auditory nerves in the cochlea and has restored partial hearing to tens of thousands of people around the world.

Others have had success with systems that trigger leg muscles so a paralyzed person can stand up or that stimulate the muscles of the hand so a person with partial paralysis can grasp an object. (The devices are activated with shoulder, arm or head movements.) Still other implants target the nerves in the eyes of blind people so they can discern light and dark and even some simple patterns.

This is dramatic stuff, although the detailed profiles of researchers and patients, as well as the nuts-and-bolts descriptions of the various technologies, might overwhelm some readers. Nevertheless, the book is a valuable introduction to an important subject. —*Kurt Kleiner*

Mind Reads



Maestro of the Mind

The Genius Engine: Where Memory, Reason, Passion, Violence, and Creativity Intersect in the Human Brain

by Kathleen Stein. Wiley, 2007 ($27.95)

As scientists continue to unlock the secrets of the human brain, the prefrontal cortex (PFC) has moved to center stage. Mounting research indicates that this brain region, situated right behind our forehead, has the power to suppress impulses and can override logical decisions when they conflict with beliefs or emotions. The PFC is the seat of genius, "the engine of choice, flexibility, decision-making, and foresight," which, Kathleen Stein argues, puts it "at the core of our humanity."

Stein, a neuroscience journalist, uses dozens of interviews with a wide range of brain scientists as the basis for her survey of recent research on the PFC's diverse functions. The book has no overarching story. Nevertheless, through a plethora of case studies and examples, Stein builds up a panoramic picture of the many roles of the PFC—from planning ahead to suppressing urges, from committing violent acts to understanding jokes.

We learn about a patient whose PFC injury affected his judgment, causing the well-educated, cultured man to slip inappropriate remarks—such as graphic details about his sex life—into professional conversations.

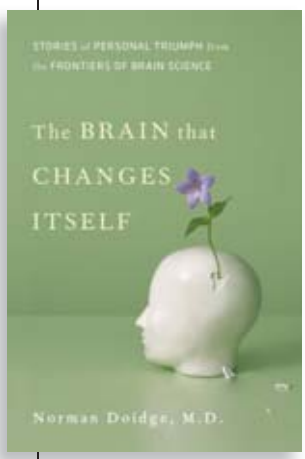
One brain-imaging study illustrates the PFC's role in inhibiting false applications of deductive reasoning. For example, scientists asked volunteers to assess the validity of the syllogism "some wars are justified; all wars involve raping of women; some raping of women is justified." They observed rapid firing of the PFC when volunteers judged the statement as false despite its presentation as a logical argument. Stein also introduces us to the PFC's function as the memory of the future. Not only is it the place where expected scenarios are first played out, it is also the center of forward-looking fantasies, such as dreams of winning the lottery or a Nobel Prize.

In the concluding chapter, "The Rise of the Machine Genius," we get a glimpse into the world of artificial intelligence. We learn that researchers have already had some success in designing machines that simulate PFC neuronal function and that have the ability to perform problem-solving and reasoning operations, which suggests these electronic brains could be harnessed to test different theories of mental disorders. Stein seems convinced that, ultimately, scientists will succeed in deciphering the complete wiring pattern of the human brain and in building a functioning replica of it. —*Nicole Branan*

Neuron Renovation

The Brain That Changes Itself: Stories of Personal Triumph from the Frontiers of Brain Science

by Norman Doidge. Viking, 2007 ($24.95)



For most of the 20th century, neuroscientists believed that adult brains, unlike those of children, could not grow new neurons or form new networks among existing brain cells. According to this view, if part of the brain were damaged or underdeveloped, the functions of that part would be lost.

But in the past couple of decades, scientists have compiled formidable evidence of the persistence throughout adulthood of neuroplasticity, the brain's capacity for structural and functional change. Sophisticated scanning technologies reveal brains to be more flexible and dynamic than traditionally thought. Moreover, new therapies and exercises draw on neuroplasticity to counteract conditions ranging from strokes and balance disorders to learning disabilities and age-related cognitive decline.

Norman Doidge, a research psychiatrist and psychoanalyst at Columbia University and the University of Toronto, recounts these developments through vignettes of the scientists, physicians and patients, as well as animal and human research subjects, at the forefront of the science of neuroplasticity. The result is an absorbing and encouraging depiction of the brain's potential to overcome debilities and diseases.

The book features protagonists such as Paul Bach-y-Rita, a University of Wisconsin–Madison physician and biomedical engineer. By placing a motion-sensing device on the tongue of patient Cheryl Schiltz, Bach-y-Rita (who died in late 2006) enabled Schiltz to regain the sense of balance she had lost as the result of inner-ear damage. The device sparked small electric charges that felt like champagne bubbles on her tongue, letting her know if she was leaning too far one way or another. In time, her brain was retrained to keep her body upright, letting her maintain her balance without the tongue device.

Other neuroplasticity pioneers discussed include psychologist Edward Taub, whose "constraint-induced" therapy involves binding the unaffected limbs of stroke patients so they will relearn to use their affected limbs; neuroscientist Michael Merzenich, whose computer-learning programs help kids with autism; and educator Barbara Arrowsmith Young, who developed mental exercises, such as reading cards with complex clock faces, to overcome her own early difficulties with abstract thought. Doidge also profiles Michelle Mack, who was born without a left brain hemisphere and whose right brain handles language functions normally done by the left.

Despite the book's ebullient subtitle, Doidge's tone is one of measured optimism. He notes that neuroplasticity also has its downsides, as when amputees' brains rewire to produce phantom pains or, more prosaically, when people learn bad habits. *—Ken Silber*

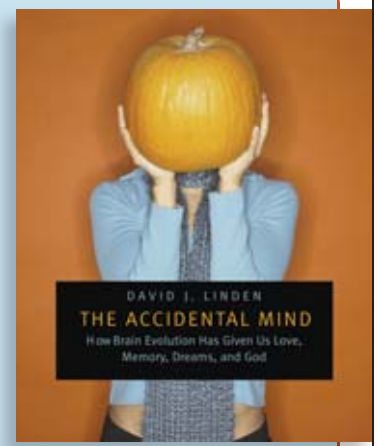
Oops, Therefore I Am

The Accidental Mind: How Brain Evolution Has Given Us Love, Memory, Dreams, and God

by David J. Linden. Belknap Press, 2007 ($25.95)

From its seat inside our skull, the brain manages our thoughts and emotions, files away our memories, makes our decisions and controls our body. Clearly, only a masterpiece of design would be capable of performing such an enormous breadth of complex tasks, right? Wrong, says David J. Linden, who contends that thinking of the brain as a beautifully engineered, optimized device is "pure nonsense."

In *The Accidental Mind,* the Johns Hopkins University neuroscientist shows us that the brain is a cobbled-together mess that was formed over millions of years of evolution. He argues that it is precisely the lack of optimized design that has led to some of our most cherished abilities: to feel love, to have memories and dreams, and to create religious concepts.



Linden's story is captivating. Chapter by chapter, he builds his compelling arguments, starting with a close examination of the human brain's structural flaws and the shortcomings of its parts. The ancient design of our neurons makes them slow and inefficient processors, he contends, so the brain requires an extraordinary amount of them and needs to interconnect them with even more synapses. The brain's neuronal network is too big to have its point-to-point wiring diagram explicitly encoded in our genes, which is why we are born with only a moderately developed brain and have to complete the fine-scale wiring by learning from experience during our species' unusually long childhood. That alone, Linden asserts, is the reason for the existence of our memories and, ultimately, for the development of our individuality.

Religious thought and practice, Linden reasons, result from the general tendency of our brain to mess with incoming data to create coherent, gap-free stories. Our brain makes visual perception seem continuous and flowing, for example, even though the pictures our neurons receive through our rapidly jumping eyeballs are not. Linden believes that it is solely because of poor brain design that this narrative-constructing function is turned on at all times, whether it is relevant for the particular task at hand or not.

In a situation where we lack evidence or a logical explanation—when contemplating the reason for our existence, say—we are driven to invent one, even if it leads humanity to appeal to a supernatural, godly power. *—Nicole Branan*

askthe**Brains**

Why is it that after listening to music, the last song you hear sometimes replays in your mind for several minutes after the music stops?

—Dave VanArsdale, via e-mail

Andrea Halpern, professor of psychology at Bucknell University, offers this explanation:

TUNES THAT GET STUCK in the head, evocatively called "earworms," are probably related to the more common experience of simply being able to call up from memory any familiar tune. For instance, try thinking of a song you know, such as "Happy Birthday." Most people I test in my lab claim they can do this easily, and the resulting auditory image is fairly vivid. Other scientists and I have been investigating the characteristics of these auditory images and how the brain processes them, which could help explain why some of these images replay persistently.

Familiar tunes that are stored in memory seem to retain characteristics—such as tempo or pitch—that closely match those of their real auditory counterparts. But what is your brain actually doing when you recall a song? My colleagues and I have asked people to carry out tasks involving musical imagery while we recorded their brain activity using neuroimaging. In one study we played sounds of different musical instruments and asked subjects to rate them for similarity. Then we turned off the speakers and asked people simply to imagine the instrument sounds to compare them. We saw similar brain activity in the two conditions: some parts of the auditory system were active both while hearing music and while imagining it, even though the imagined condition was silent.

As we learn more about how the brain processes tunes, we can speculate about why songs are sometimes persistent. As your question points out, earworms often occur for recently heard tunes that are fresh in your memory. The end of a catchy musical phrase reminds you of the beginning again, which can get a cycle going. And contrary to popular belief, earworms are more commonly liked, not disliked, songs. In one of our studies 40 students kept an earworm diary for two weeks. More than half the tunes were rated as pleasant, 30 percent were neutral and only 15 percent were judged unpleasant.

Most of the time the repeating tune just went away by itself—good news for people who do find their earworms annoying. And if that natural fading did not work, the respondents said that engaging in another activity usually made the earworm crawl back into its burrow.

Why doesn't the human brain have pain receptors?

—Henry Minassian, Brussels, Belgium

Mark A. W. Andrews, professor of physiology and director of the Independent Study Pathway at the Lake Erie College of Osteopathic Medicine, replies:

FOR ANY STIMULUS to be perceived, including pain, specialized cells called sensory neurons must be activated. Internal organs, such as the brain, have few of these neurons; in fact, internal organs house only about 2 to 5 percent of all sensory neurons in the body. This arrangement allows us to closely assess the world around us (possibly because most threats arise externally) while limiting our conscious awareness of internal changes.

Sensory neurons that are specialized for pain perception are known as nociceptors (from the Latin *nocere*, "to hurt"). The highest concentrations of nociceptors are found in the areas of our bodies that act as direct links to the outside world, such as the skin, bones, joints and muscles. Here the pain receptors act as border sentries, warning us of possible damage so that we may attempt to escape from further harm.

Contrary to popular belief, tunes that get stuck in our heads are more commonly liked, not disliked, songs.

Nociceptors do exist near the brain in its blood vessels and in the meninges, the three thin membranes that wrap around and protect the brain and spinal cord. Recent research has shown that migraine headache pain may arise from the nociceptors in the meninges. Other internal body parts also tend to have their nociceptors in the surrounding tissue, alerting us if they are stretched or squeezed. Interestingly, if the few nociceptors within an organ are stimulated, the pain is "referred" to regions on the surface of the body. This phenomenon explains why the pain that may accompany a stroke is commonly felt in muscles and joints, particularly in the shoulder region. Although the stroke is damaging the brain, the victim does not sense the pain in the brain itself. M

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

DEBRA COOK-BALDUCCI (*top*); COURTESY OF MARK A. W. ANDREWS (*bottom*)

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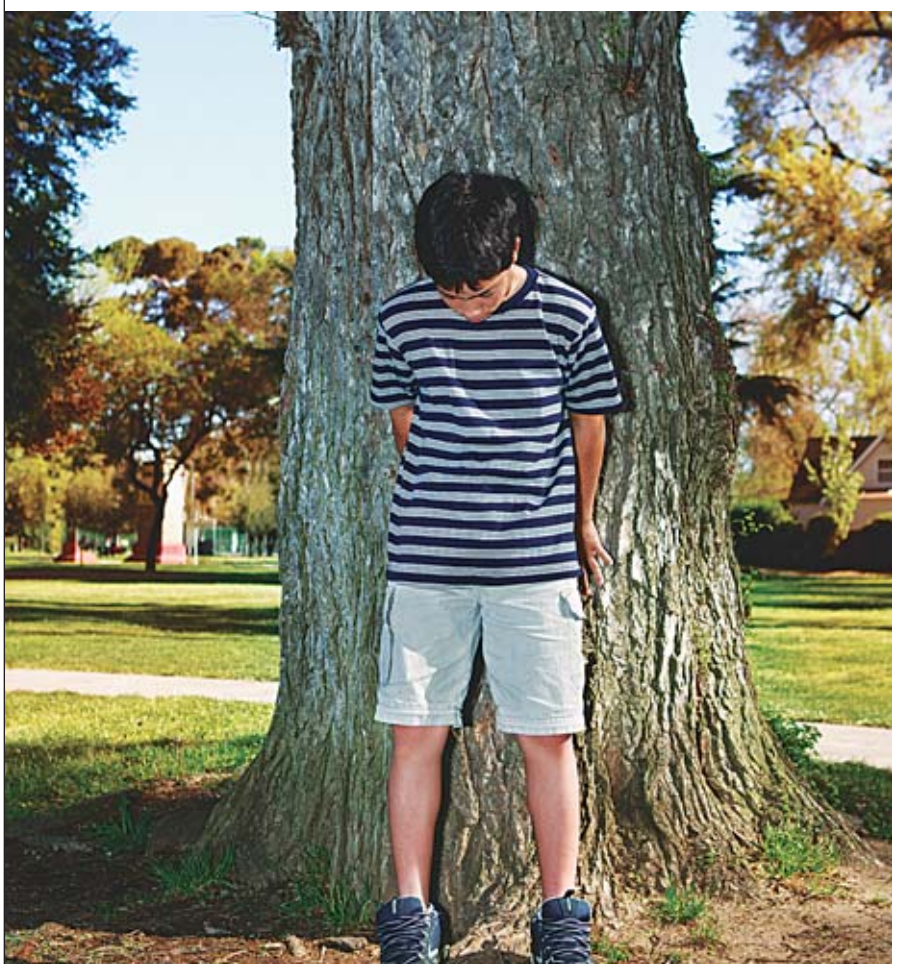

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JOSON *zefa/Corbis (left)*; GETTY IMAGES *(right)*

Head Games

Match wits with the Mensa puzzlers

1 Fill in the blanks surrounding the letters I C E D, according to the clues.

a) _ _ I _ C E D **Clearly indicated**

b) I _ C E _ D _ _ _ _ **Fiery**

c) _ _ _ I C E D **Joined two tapes**

d) _ _ _ _ I _ C E D **Made a believer of**

e) I _ C _ E D **Longed**

f) _ I C _ E D **Witches of Oz—the musical**

g) _ I _ C E D **Finely chopped**

h) _ _ I C _ E _ _ D **Ratcheted up**

i) _ _ I _ C _ E D **Exchanged**

2 Each letter stands for a different digit. Determine their values to make all five of the equations true.

MOM × D = DAD **D + A + D = 10**

DAD × A = MIND **M + I + N + D = 15**

M + O + M = 5

3 Take one of the planets in our solar system, change one of its letters, then rearrange those letters to get another planet. What are the two planets?

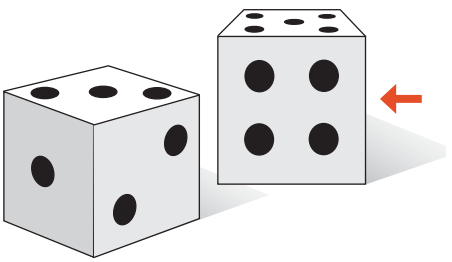
4 A farmer has three hens named Anna, Belle and Carol. On any given day a hen can lay either one egg or no eggs. No hen can lay eggs for three days straight, but no hen would ever go two days in a row without laying an egg. In addition, each hen has a particular way of clucking. Anna will cluck only when she has laid an egg. Belle will cluck only when she has not laid an egg. Carol will cluck only when either zero or two eggs have been laid in the henhouse that day. Over a three-day period the farmer hears the following: on the first day only one hen is clucking, on the second day two hens are clucking, and on the third day all three hens are clucking. How many eggs in total did the hens lay?

5 What do these four words have in common?

WORTH **FAST**

ZEST **MOUTH**

6 On the standard dice shown (on which opposite sides of a die total 7), what number must appear on the hidden die face to which the arrow is pointing?



7 Place the six U.S. Army ranks below in order from highest to lowest. When the ranking order is correct, the underlined letters will spell out a word appropriate to this military theme. What is it?

Sergeant

Major general

First lieutenant

Four-star general

Private

Colonel

8 Start at any letter and jump to an adjacent letter, either horizontally, vertically or diagonally, spelling out the name of an animal. Find eight animals.

N	A	T
R	O	I
E	G	L

American Mensa is at www.us.mensa.org/sciamm

Answers

1. a) EVINCED b) INCENDIARY c) SPLICED d) CONVINCED e) ITCHED f) WICKED g) MINCED h) QUICKENED i) SWITCHED

2. M = 1, D = 2, O = 3, I = 5, A = 6, N = 7.

3. Saturn and Uranus.

4. The hens lay six eggs in three days.

	Anna	Belle	Carol
DAY 1	0 eggs	1 egg	1 egg
DAY 2	1 egg	1 egg	0 eggs
DAY 3	1 egg	0 eggs	1 egg

5. Change the first letter of each word to get the four directional points: north, east, west and south.

6. 1.

7. Salute. (Four-star general, major general, colonel, first lieutenant, sergeant, private.)

8. Ern (a bird), goat, lion, tiger, rat, rail (another bird), liger (offspring of a lion and a tigress), and tigon (offspring of a tiger and a lioness).