

# S T A N F O R D M E D I C I N E

Spring 2012

special report

## INSIDE THE HEAD

THE FUTURE OF  
PSYCHIATRY

### Zapping the blues

High-tech depression treatment

### Home lab

Parents assess autism therapies

### Oliver Sacks

The mind sleuth

### Constant craving

Understanding the addicted mind

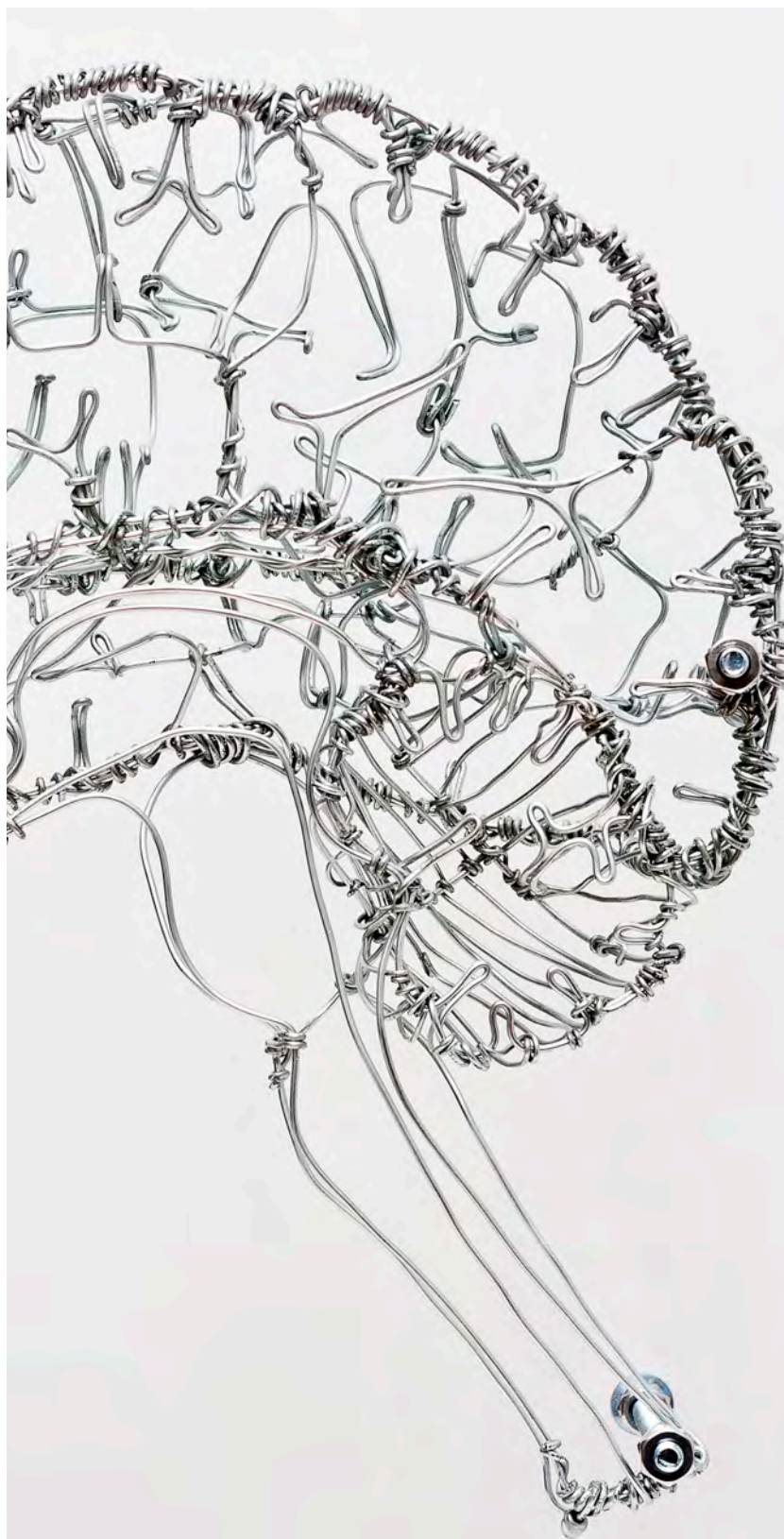
plus

### In transition

Helping transgender patients

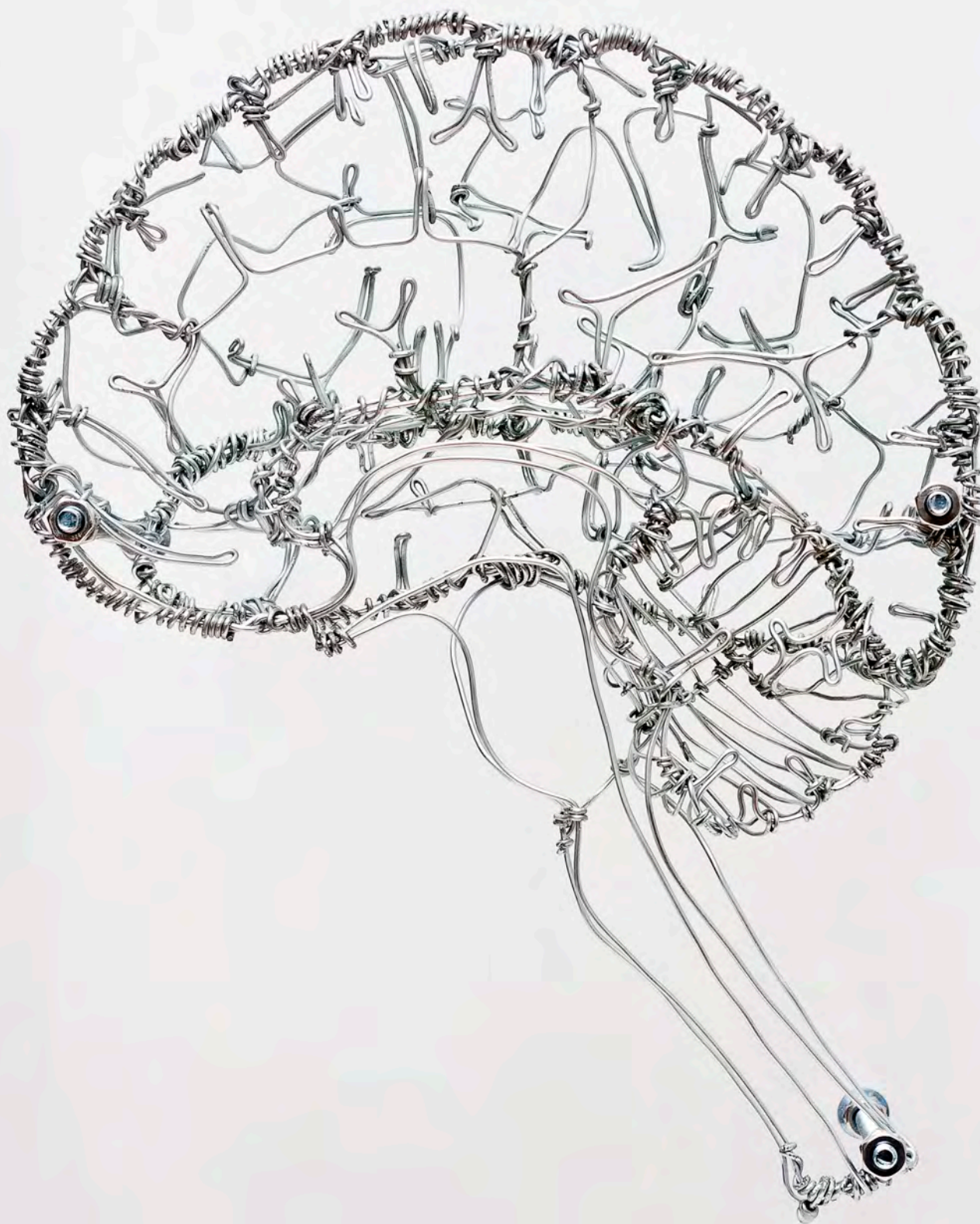
### Big bangs

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S T A N F O R D  
M E D I C I N E

Spring 2012





# GOOD GRIEF

## CAREGIVERS SHARE SORROW

He was just barely out of his teens, full of youthful promise, when he and his parents arrived at Stanford Hospital. He died a year later of leukemia. Something about this kid got to the professionals who cared for him through those months, something that brought them to tears more than once as they watched him deteriorate. • A few months later, more than 120 medical professionals packed into a Stanford Cancer Institute conference room, and one by one they recalled experiences with this patient, and tears flowed again.



"I didn't want to deal," said one physician, after telling the group that the day the young man was sent home for the last time he left the unit to avoid seeing him. "And the thing I've done to deal with this is zero — until this meeting."

Since fall 2011, Stanford has become one of 245 hospitals and health-care institutions to adopt Schwartz Rounds, a regularly scheduled time to discuss social and emotional issues that arise in caring for patients. After listening to a panel's short presentation on a case or topic, caregivers respond with their own perspectives. At Stanford the sessions take place every two months.

"We wanted to provide a place where people could speak their emotions in a safe environment, without censure, as a catharsis," says Sridhar Seshadri, the hospital's vice president in charge of the cancer center.

The rounds are the brainchild of the Schwartz Center for Compassionate Healthcare, a nonprofit founded by health-care attorney Kenneth Schwartz shortly before his death in 1995 from lung cancer. The organization's mission is to advance compassionate health care, and the Schwartz Rounds are its centerpiece.

"In some ways, feelings have taken second place to the illness and the technology," says Douglas Blayney, MD, the Ann & John Doerr Medical Director of the Cancer Institute. "Patients often have a support network. We in the profession don't often have an opportunity to share with one another, to know what our colleagues are feeling and how they are coping."

But a body of research (as well as common sense) reveals that those who give care need care, too, and that lack of it contributes to burnout. Finding that care, or even acknowledging a need for it, has been difficult in medicine, a culture that tends toward bravado. "In Schwartz Rounds, you find counsel in everyone else," says Julie Latini, patient care manager of the hematology/oncology unit at the hospital. "We get insight on how to cope better."

"We want to come up with new strategies to care for ourselves better so we can care for our patients better," says Kavitha Ramchandran, MD, medical director of Stanford's supportive oncology program. "This is a chance for us to be open and honest with one another, to talk about the human impact on us of caring for patients with devastating illnesses." — SARA WYKES

# S T A N F O R D M E D I C I N E

## SPECIAL REPORT

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**Though psychiatric disease is considered a disorder of the brain, the ability to understand mental illness at the level of the brain's disordered molecules and neural networks is only now emerging.**

We see this with Ricardo Dolmetsch, a member of our faculty who has a child with autism. He has converted skin cells from people with a type of autism into stem cells, then converted these into brainlike balls of neurons. By studying these neurons, he has determined some ways in which these cells are distinctive, and has found a drug that corrects the abnormalities in vitro. He describes what he's done as creating a human behavioral disorder in a petri dish — or at least the ability to more deeply study it that way. • This approach could transform behavioral and mental health research, as Thomas Insel, MD, director of the National Institute of Mental Health, explains in a recent blog post: “This would be the stuff of neuroscience fiction — if it weren't real. This is nothing less than a way to reprogram a patient's easily obtained skin cells into his or her own neurons, theoretically allowing us to fathom the secrets of that specific individual's disorder. And, perhaps someday, to use the information to inform that patient's treatment — or maybe even engineer a one-on-one personalized treatment.” • This leap forward is not just happenstance. Decades of creative and painstaking basic research funded by federal and state agencies have made these advances possible. In the case of Professor Dolmetsch's work, funding for stem cell research was particularly valuable.

While a national political debate swirls, scientists are making discoveries about stem cell development that are leading to tools for psychiatric research. At Stanford, we're leaders in the emerging science of neuronal stem cell biology.

Marius Wernig and Gerald Crabtree, two of our faculty who also happen to be friends and neighbors, amazed the biomedical world by independently developing two different methods of converting skin cells directly into neurons, skipping the stem cell stage entirely. Indeed, when Professor Crabtree looked through his microscope and saw neurons, he didn't believe what he was seeing. They published their discoveries within a few months of each other last summer.

Researchers throughout the world are pursuing similar strategies to study a range of illnesses involving the brain, including schizophrenia and Parkinson's disease. Their accomplishments are not only extraordinarily useful for testing potential treatments and studying the intricacies of brain cells, they're a testament to the power of science.

When you consider that we can transform an ordinary skin cell into the elaborately branched architecture typical of a neuron, and that the resulting cell functions as a neuron should, incredible new insights and discoveries seem possible. The important connections between investments in basic research and their impact on health and disease also become more apparent.

In this issue you'll read how new understandings about the brain are influencing psychiatry. You'll also see that we are far from grasping all the answers. But the amazing developments in our laboratories give us reason to believe that many of those answers are on the horizon. They underscore the importance of continued investments in basic science research.

Sincerely,  
Philip A. Pizzo, MD  
Dean

Stanford University School of Medicine  
Carl and Elizabeth Naumann  
Professor, Pediatrics, Microbiology  
and Immunology



# upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD UNIVERSITY MEDICAL CENTER

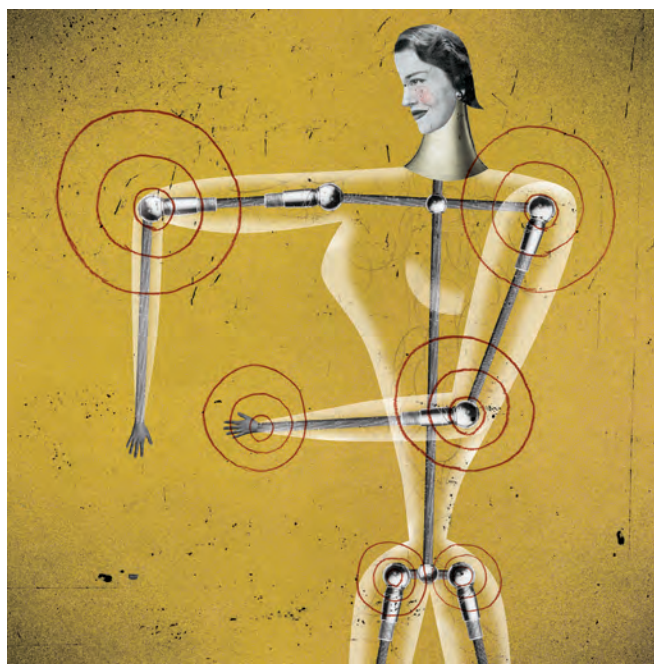
## Joint discovery

A STUDY OF JOINT PAIN HAS OPENED UP A NEW ROUTE to treatments that could stop the inexorable advance of osteoarthritis, which affects 30 percent of people over age 60.

"People in the field predominantly view osteoarthritis as a matter of simple wear and tear, like tires gradually wearing out on a car," says associate professor of immunology and rheumatology William Robinson, MD, PhD, who published the study in the December 2011 issue of *Nature Medicine*. It also is commonly associated with blow-outs, he adds, such as a tear in the meniscus or some other traumatic damage to a joint.

But researchers noticed that inflammatory cells and some of the substances they secrete were higher than normal in osteoarthritic joint tissues, even before symptoms were evident. That got Robinson and his co-authors thinking that inflammation might be a driver, rather than a consequence, of the disease.

Their new study showed that, indeed,



initial damage to the joint starts a chain of molecular events that escalates into an inflammatory attack on the damaged joint by one of the body's key defense systems against bacterial and viral infections, the so-called complement system. This sequence of events triggers a chain reaction called the "complement cascade," and it begins early in the development of osteoarthritis.

Drugs thwarting inflammation induced by the complement system may someday prove useful in preventing the onset of osteoarthritis after an injury, says Robinson, a staff physician with the Veterans Affairs Palo Alto Health Care System. Toward that end, he has begun a pilot study of the effects on osteoarthritis of an anti-inflammatory drug that's already available. — BRUCE GOLDMAN

**4.6%**  
of U.S. GDP was health spending in 1950. In 2009, it was above 17%. More on the health economy: <http://stan.md/GEKehR>.

## Anthrax variations

STANFORD

RESEARCHERS HAVE discovered that people vary widely in their sensitivity to the anthrax toxin, which could explain why some weather infection by the deadly bacterium *Bacillus anthracis* with no symptoms.

Their study, which looked at blood cells collected from 234 people, found that cells of three people were virtually insensitive to the toxin, while the cells of some were hundreds of times more sensitive than those of others.

The study was published Feb. 21 in the *Proceedings of the National Academy of Sciences*.

More at <http://stan.md/xBGQUS>.

— KRISTA CONGER





## Log on

Think of it as Facebook for Stanford's medical minds. The School of Medicine now has a social network of its own. The school's information technology team believes it's the first fully deployed social network at any U.S. academic medical center.

The network, launched in October, combines the medical school's Community Academic Profiles system, known as CAP, with a collaboration platform that allows users to share status updates, customize profiles, follow colleagues, form groups, share documents and even find research collaborators and mentors. CAP

Network provides full profiles for all students, faculty and staff at the School of Medicine, bringing the total number of individuals in the system to nearly 10,000. So far, about half of the group's members have activated their accounts.

"The users of CAP Network will be bound by a 'social-networking honor code,' based on university policies," says Henry Lowe, MD, senior associate dean for information resources and technology. "Operating within that framework, we leave it to the community to decide how they want to use CAP Network on a day-to-day basis. It should be interesting to see how they use the platform."

Visit <http://cap.stanford.edu>.

— JOHN STAFFORD

## WOMEN FEEL MORE PAIN?

WOMEN REPORT MORE INTENSE PAIN than men in virtually every disease category, according to Stanford investigators who mined a huge collection of electronic medical records — 160,000 pain scores reported for more than 72,000 adult patients.

"We saw higher pain scores for female patients practically across the board," says Atul Butte, MD, PhD, the senior author of the study, published in the March *Journal of Pain*.

"In many cases, the reported difference approached a full point on a 1-to-10 scale. How big is that? A pain-score improvement of one point is what researchers view as indicating that a pain medication is working."

However, it's not clear that women actually feel more pain than men do, says Butte. "But they're certainly reporting more pain than men do. We don't know why. But it's not just a few diseases here and there, it's a bunch of them — in fact, it may well turn out to be all of them. No matter what the disease, women appear to report more intense levels of pain than men do." — BRUCE GOLDMAN

## Computing cancer

SINCE 1928, THE WAY BREAST CANCER characteristics are evaluated and categorized has remained largely unchanged. It is done by hand, under a microscope. Pathologists examine the tumors and score them according to a scale first developed eight decades ago. These scores help assess the type and severity of the cancer and calculate the patient's prognosis and course of treatment.

Now computer scientists and pathologists at Stanford have trained computers to analyze breast cancer microscopic images better than humans can. They report this in the Nov. 9, 2011, issue of *Science Translational Medicine*.

Humans, in the form of pathologists, use three specific features to evaluate breast cancer cells — what percentage of the tumor is comprised of tube-like cells, the diversity of the nuclei in the tumor's outermost cells, and the frequency with which those cells divide.

On the other hand, the program, called C-Path, assesses 6,642 cellular



factors to reach its conclusions. C-Path yielded results that were a statistically significant improvement over human-based evaluation.

"We're looking at a future where computers and humans collaborate to improve results for patients across the world," says Matt van de Rijn, MD, PhD, a professor of pathology and co-author of the study. The study's lead author was Andrew Beck, MD, a doctoral candidate in biomedical informatics.

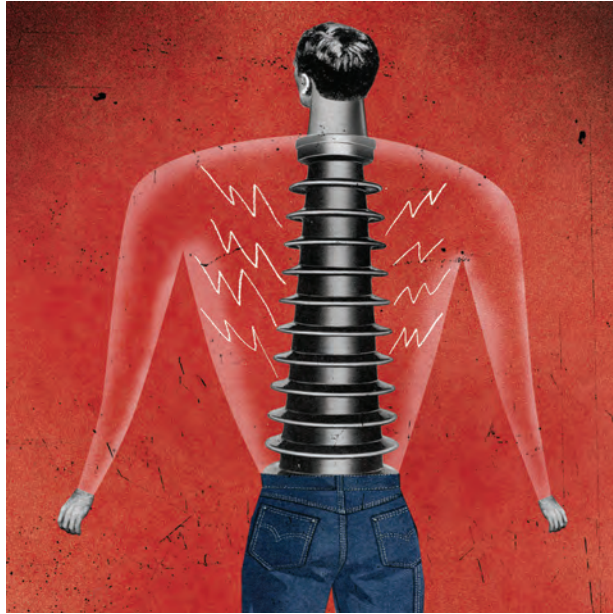
— ANDREW MYERS

# Historic trial halted

"SPENDING PERSIAN NEW YEAR WITH FAMILY. I CAN'T COMPLAIN. I'M ALIVE, RELATIVELY HEALTHY, AND LOVED :)," TWEETS 23-YEAR-OLD KATIE SHARIFY IN MARCH, FOUR MONTHS after she became the fifth and final participant in a study of an embryonic-stem-cell-derived treatment for severe spinal cord injury. • Sharify, paralyzed from the waist down in a car accident, learned on Nov. 14, 2011 — just two days before her treatment — that the multisite trial's sponsor, Geron Corp., was ending the trial early for financial reasons. They had initially planned to enroll eight to 10 patients. • "At that point I felt very let down and didn't know if I wanted to go forward with the procedure," recalled Sharify in a December interview. "But then I decided that five patients were still better than four, and that I could still have some sort of an impact." • Stanford's chair of neurosurgery, Gary Steinberg, MD, PhD, performed the procedure at Santa Clara Valley Medical Center on Nov. 16.

The Geron trial was the first to implant cells derived from human embryonic stem cells into human patients. As a trial participant (the second at Stanford), Sharify received an injection of about 2 million specialized cells to the injured area of her spinal cord. The cells, oligodendrocyte precursors, had been coaxed to develop from human embryonic stem cells. Damage to the sheath of oligodendrocyte cells that normally wraps nerve cells is a common cause of paralysis. The trial was the first phase of an effort to see whether the cells could repair the damage. The patients will be monitored for the next 15 years, according to the company.

The trial's end is a disappointment but not a calamity, says Steinberg. "We should remember that five of the anticipated eight total patients were successfully transplanted with no adverse effects noted to date. Since this was designed as a safety study, the outcomes are very encouraging." — KRISTA CONGER



## TWINS SEPARATED

GINADY SABUCO HAS TO RUN TO KEEP UP WITH HER TWIN TODDLERS, Angelina and Angelica, who are racing around a San Jose, Calif., park in opposite directions. • She's not complaining, though. • The girls, now 2 1/2, were born joined at the chest and abdomen with fused livers, diaphragms and breast bones. The chance for them to grow up as individuals is a dream come true, she says. • During a 10-hour surgery at Lucile Packard Children's Hospital on Nov. 1, 2011, the twins' sternums were completely removed and reconstructed with resorbable plates that will gradually dissolve as the bones take over.

Recovery was faster than expected, with the girls going home Nov. 15 and walking independently less than a week later. Their balance and strength have continued to improve.

The girls have distinct personalities: Angelina is quiet, Angelica more talkative. They still love playing together and wearing matching dresses, but as their happy parents are discovering, they also like exploring on their own. — ERIN DIGITALE



## Blowing smoke

TOBACCO COMPANIES CONDUCTED a decades-long campaign to manipulate throat doctors into calming the public's concerns that smoking harmed health, according to a new study by Stanford researchers. Starting in the 1920s, this campaign continued for over half of a century.

"The companies successfully influenced these physicians not only to promote the notion that smoking was healthful, but actually to recommend it as a treatment for throat irritation," says the study's senior author, Robert Jackler, MD, professor and chair of otolaryngology.

Jackler and co-author Hussein Samji, MD, published the study in January's *The Laryngoscope*.

— TRACIE WHITE

A conversation with Robert Jackler about physicians working for Big Tobacco: <http://stan.md/waYz7M>



# brain power

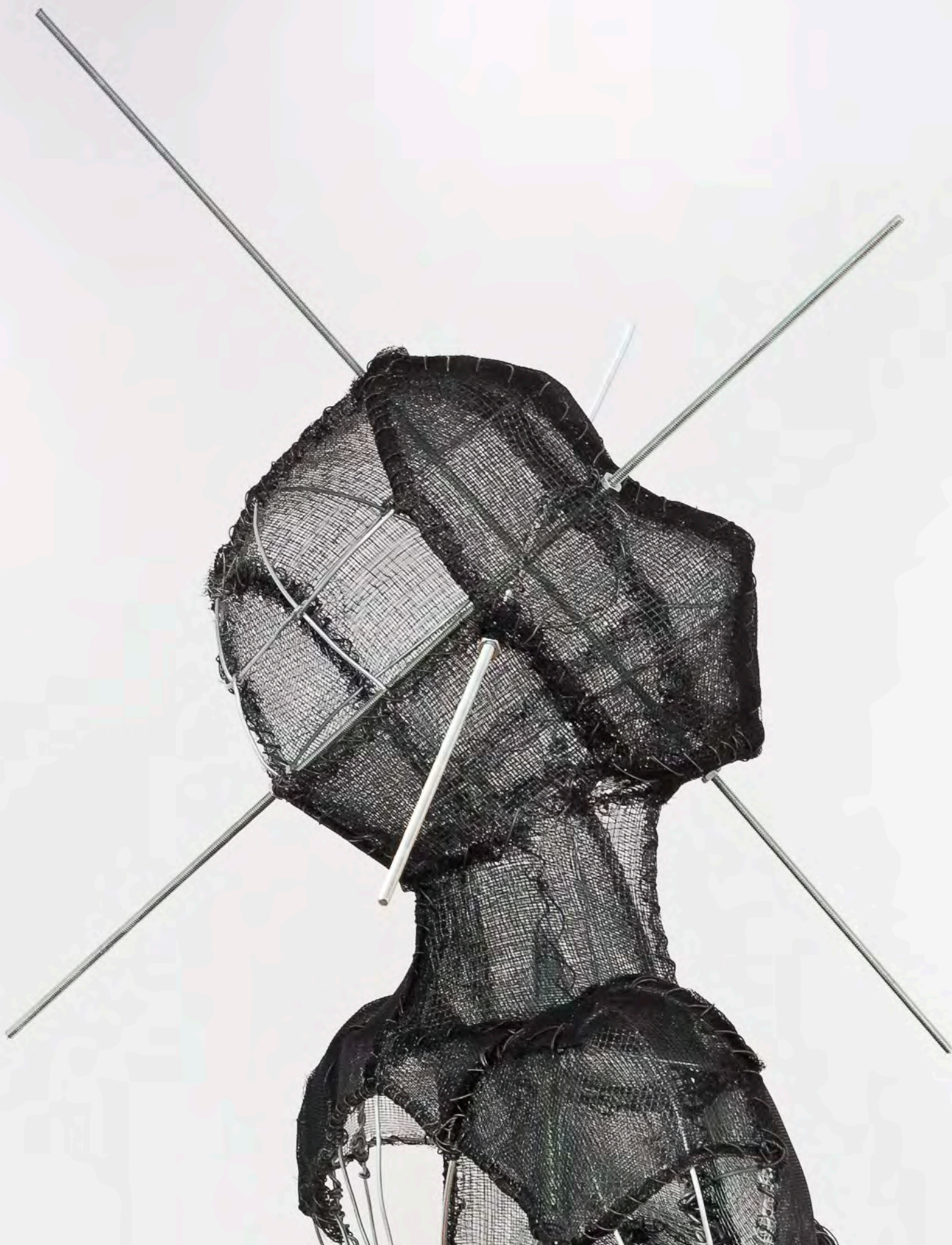
## PSYCHIATRY TURNS TO NEUROSCIENCE

**My head is  
clamped into a padded capsule to  
keep it stable as researchers measure my brain activity.  
I am lying on my back inside a functional  
magnetic resonance imaging machine, and any movement could muddy  
the results. There is a strap around my chest to record my  
breathing rate. Sensors on my fingers monitor my sweat — and I fear that I am sweating a lot.**

On a screen in front of me flash a series of strange black-and-white photographs of smiling and terrified faces. Each has the word “happy” or “fear,” in red capital letters, superimposed across it. Sometimes the word matches the expression; sometimes it doesn’t. I am supposed to push one of two buttons if the face looks fearful, and the other if it’s happy. The task sounded easy enough before the scan started. Now I find myself freezing, struggling to identify an expression that is at odds with the word. A new picture appears every few seconds, and I am beginning to feel dizzy, my eyes starting to water. • Dozens of people have done this particular facial-identification exercise with an fMRI machine measuring changes in the blood flow inside their brains. The data accumulated from their responses is revolutionizing how we define and treat anxiety, depression and other emotional disorders. It’s part of a new wave of fMRI studies, genetic research and biomolecular work that are grounding psychiatry in neuroscience, a longtime yet elusive goal for many psychiatrists, since the start of the profession in the late 19th century. • At present, the diagnosis of mental illness and its treatment are based almost entirely on clinicians’ observations and their patients’ reports. But many psychiatrists yearn to identify the biological etiology of mental illness — to pinpoint how abnormal brain function

BY JONATHAN RABINOVITZ

SCULPTURE BY FEDERICO CARBAJAL RAYA



causes psychiatric symptoms — and to develop treatments targeted to fix these broken mechanisms. It's the difference between feeling a patient's forehead to check for fever or doing a blood test to identify the bug that's causing the high temperature so you can prescribe an antibiotic.

"The current approach never gets to the brain mechanisms that lead to symptoms — there's no external validation," says Amit Etkin, MD, PhD, who with another researcher devised the test I am taking in the fMRI. "We're changing that."

For roughly a decade, Etkin, 35, an assistant professor of psychiatry and behavioral sciences at the Stanford University School of Medicine, has been pioneering the use of fMRI scans to reveal how brain activity differs in healthy people compared with those suffering from mental illness. The face-expression test I am taking is one of several innovations that have allowed him and others to detail the regions of the brain that function abnormally in people with anxiety, post-traumatic stress disorder and depression.

"Amit is a poster child for how neuroscience can inform psychiatry," says Nobel laureate Eric Kandel, MD, PhD, a neuroscientist and psychiatrist who also happens to have been Etkin's graduate advisor at Columbia University's medical school. "By turning to imaging early on, Amit showed that we can use it not only to study normal responses to emotion but also abnormal responses — conscious and unconscious — and start to localize where in the brain they occur."

The effects of neuroscience on psychiatry, of course, go beyond Etkin's work in imaging anxiety-related disorders, ranging from the improved knowledge of the neuropathology of many other mental illnesses such as addiction [see story p. 24] to the development of such new treatments as transcranial magnetic stimulation and deep-brain stimulation for depression [see story p. 12]. Etkin's work is also part of a broader movement to develop new ways to provide therapy to people with mental illness [see story p. 18].

are receiving treatment. Anxiety is the most pervasive of all mental disorders, says Etkin, and his work has been critical to redefining it in biological terms.

I wanted to understand how Etkin's work is changing the way that psychiatry looks at mental illness, and so on this February morning I am inside the fMRI machine, hoping to grasp what exactly Etkin's face-expression exercise elicits.

I cringe at incorrect responses that happen before I have time to think, and marvel at the many correct ones that seem to occur automatically. I am relieved once I'm done, though I'm worried about what my results will reveal. These scans are not accurate enough to be diagnostic, but still I fret: Are the images going to show a brain rife with anxiety?

Are my fMRI pictures normal?

**"Why should psychiatrists care about neuroscience?" • That's the title of a talk that Etkin gives at the start of a new neuroscience course for third-year psychiatry residents at Stanford that he has developed with the support of department chair Laura Roberts, MD.** The lecture begins with a blunt discussion of the state of the profession. "Turns out we're not terribly good at treating psychiatric diseases (worse, likely, than we have thought)," reads one PowerPoint slide. Another bullet point notes, "We also don't understand how our current therapies work, for whom are they likely to work, and why." Next comes one word: "Yikes!"

Over the last half-century, other fields of medicine have experienced a decline in mortality and disability rates as new devices and treatments have been developed, but psychiatry has lagged behind, says Etkin, who is also an investigator at the Mental Illness Research, Education and Clinical Center at the Veterans Affairs Palo Alto Health Care System. For instance, while the number of drug classes for cardiovascular disease has increased since the 1950s from two to 16, the number for depression and schizophrenia has barely budged, increasing from four to five. To

## 'Turns out

### **WE'RE NOT TERRIBLY GOOD AT TREATING PSYCHIATRIC DISEASES.'**

There certainly is a need for some new approaches. Mental health disorders are, by some accounts, the leading cause of disability in the United States and Canada, and the U.S. Centers for Disease Control and Prevention estimate that a suicide occurs every 15 minutes. According to one recent federal report, about one-half of Americans will have a serious mental health condition during their lifetimes, and at present, fewer than 50 percent of those with such conditions

make matters worse, current psychiatric treatments aren't terribly effective. A definitive study on schizophrenia treatment shows that people with this disease typically go off their medications after six to nine months because they were not sufficiently effective, and the side effects are dreadful. A major investigation into the efficacy of several antidepressants revealed that only 43 percent of the study participants got well and stayed well.

The comments Etkin received from residents after the



lecture indicate that it was an eye-opener for many, with at least one finding it downright discouraging. (“This is a real downer,” read the comment on the feedback form.) “I try not to paint a horribly bleak vision,” Etkin says, “but this is reality; they need to be in touch with it.”

Etkin’s talk is based on a similar presentation given by National Institute of Mental Health director Thomas Insel, MD, who also does not mince words about the present state of affairs. “Current treatments are not effective enough,”

Medicine revamped its curriculum to emphasize neuroscience when studying psychiatric cases.

And at Stanford, Roberts and Etkin have ushered in the neuroscience course, which is now in its second year. Beyond this, Roberts is introducing subspecialty clinical training programs that encourage young psychiatrists to develop deep expertise in addiction, psychosomatic medicine and forensic psychiatry, along with the existing subspecialty of child and adolescent psychiatry. No matter what their specialty, she wants Stanford

## ‘We need

**TO HUG THE SCIENCES, AS  
THAT’S THE KEY TO THE FUTURE.’**

he wrote last year on his blog. “Briefly stated: in many cases patients receiving the best of current care are not recovering.”

This urgency to develop new treatments comes amid worries that psychiatry has become less appealing to many young doctors choosing a specialty. From 2000 to 2008, the number of psychiatry residency graduates declined from 1,142 to 985, according to a study last year in *Academic Psychiatry*. Over the last few years, the trend appears to be improving but nowhere near fast enough to keep pace with the need — or the increase in many other medical disciplines. From 2007 to 2011, for example, there was an increase of 40 first-year resident positions in psychiatry compared with 319 in emergency medicine.

The difficulties in attracting new talent can also be chalked up to other problems. For one, the financial rewards of psychiatry have diminished relative to many medical disciplines. While the field attracts young doctors excited about psychotherapy, they have fewer opportunities to be reimbursed for such work as less expensive practitioners, such as social workers and counselors, increasingly take the cases. And questions about the effectiveness of blockbuster psychotherapeutic drugs, once promoted as cures for all, have undermined the profession’s reputation and led to charges of undue influence by pharmaceutical companies.

“The profession,” says Insel on his blog, “is struggling with its identity.” Insel believes the way to resolve that is through a greater focus on neuroscience, which, he says, will draw a new generation of psychiatrists. A nationwide survey that Etkin helped conduct for the NIMH confirms its allure: Roughly nine of every 10 residents agree that there should be more neuroscience in their training.

In response, the NIMH is offering psychiatry residents the opportunity to enroll in its annual Brain Camp, which instructs them in the most recent findings from cognitive science, neuroscience and genetics. The Yale School of

psychiatry residents to become literate in fMRI results, genetic tests and molecular biology, and the neuroscience class is a step in that direction. “We have to help bridge the disconnect between the latest research advances and what occurs in the everyday practice of clinical psychiatry,” Roberts says.

Roberts sees the neuroscience class as evidence of how psychiatry is moving beyond the historic split between two camps. On one hand are those espousing biological treatment (she sums up how it’s been viewed as “up-to-date and scientific” but also may be perceived as “reductionistic, impersonal and tainted”). On the other hand are those favoring psychotherapy (it’s been seen as “compassionate and valuable but also may be perceived as unproven, touchy-feely and ‘old school,’” she says). She believes that advances in genetics and neuroimaging are already bridging the gulf: Science and therapy can be used to make each other more effective, she says. “We need to hug the sciences,” she tells me in an interview, “as that’s the key to the future — that’s where we discover new ways of understanding neuropsychiatric disease as well as its prevention and optimal treatment.”

But by treatments, she doesn’t just mean medications. “I can’t imagine a future where psychiatry does not also involve therapy,” she says. “Psychiatry involves the underlying therapeutic relationship, as well as the insights drawn from the neurosciences; it’s the combination of the two that will lead to better outcomes in the future.”

**A week before doing my fMRI, I go online to try a series of computer games that Etkin is testing for the treatment of depression and anxiety. One is an arithmetic challenge requiring me to solve equations before they disappear from the screen; some involve quickly evaluating facial expressions; another requires that I click on bubbles floating around the screen that have a word describing a positive**

emotion. I feel some pleasure as I hear the “pop” from selecting “joyful” and “love,” while allowing bubbles for “fury” and “sulky” to drift away.

It takes about 40 minutes to complete these exercises, which were created by two companies. There are many more such games that have recently emerged as part of a new therapeutic approach known as cognitive bias modification, which aims to change behavior and rewire the brains of people who are depressed or anxious.

workout, but Gyurak assures me that this lack of awareness is part of the plan, that the exercises help reframe emotion processing without your knowing it. A key aspect of Etkin’s research is that he’s focusing on “implicit” emotion regulation — a different way of thinking about what Sigmund Freud referred to as the unconscious. The point is that the neurocircuitry underlying psychiatric disorders operates without our knowing about it; these disorders typically involve deeply ingrained, dysfunctional emotional

## The idea is to see if the **EXERCISES ENHANCE ACTIVITY IN THE REGIONS OF THE BRAIN CRITICAL FOR EMOTION REGULATION.**

While some suggest that CBM might substitute for psychotherapy, Etkin does not believe that computers are going to replace therapists. “The utility of psychotherapy is proven without a shadow of a doubt,” he tells me, and neuroscience research is beginning to show why this is so. According to a review in *Psychiatric Times* in August 2011, there are at least 19 imaging studies that show psychotherapy alters brain function in patients suffering from major depressive disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder, specific phobias, post-traumatic stress disorder and borderline personality disorder.

This doesn’t mean, however, that psychotherapy alone is the answer. As Etkin notes, it’s not an option for most people because insurance doesn’t cover it, and there are not nearly enough practitioners to serve all the people who might avail themselves of it. What’s more, many people don’t want to do it.

So Etkin and others are looking for alternatives, including the computer games. In the study now under way in his lab, people with depression and anxiety undergo fMRIs before and after weeks of playing these games. The idea is to see if the exercises enhance activity in regions of the brain critical for emotion regulation, just as an athlete’s workout might be designed to build key muscles.

“If you do curls over and over, your biceps get stronger,” says Anett Gyurak, PhD, a postdoctoral scholar in Etkin’s lab who is overseeing the study. “So we’re trying to do that — train the muscle for emotion regulation.” The results so far suggest that changes are, in fact, occurring in both brain activity and how people feel; future research could help develop even more effective exercises. Indeed, Gyurak, Etkin and psychiatry professor Alan Schatzberg, MD, have just filed a patent for a game that they believe is better designed to stimulate the neurocircuitry involved in emotion regulation.

I have no idea that I have just completed a vigorous

habits. One of the notable advances in the neuroscience of psychiatry, thanks in part to Etkin, is that we can now image — and identify — the neural networks behind such implicit emotions and thus see how interventions, whether they be drugs, psychotherapy or computer games, may change them.

**“I came into psychiatry as a neuroscientist,” says Etkin, who has a doctorate in neuroscience as well as an MD. “It’s a perspective that serves me well.”** In 2010, when he joined the Stanford faculty, he established his lab, which now has 23 people and grants totaling \$4.25 million. While his job is technically 100 percent research, he sees patients every Tuesday afternoon. The son and grandson of scientists, he is also married to a psychiatrist. On a wall in their house they have his-and-her fMRI scans of their brains.

Etkin is not the sort of professor you would likely have found in an academic psychiatry department a few decades ago. Back then, the research tools were still too rudimentary to shed light on how feelings and behavior are rooted in the brain; besides, many in the psychiatric establishment viewed such research as irrelevant: The thinking was that social and environmental factors were at the heart of most mental illness.

But by the late 1990s a sea change was beginning, with the advent of new imaging techniques, developments in molecular biology and the promise of genomic sequencing. Etkin was swept up in the tide. He chose to go to Columbia so he could study with Kandel, who in 2000 was awarded his Nobel for showing how molecular changes in synapses lead to the formation of memory. Kandel has been at the forefront of calling for a rapprochement between psychiatry and biology, particularly neuroscience. In 1998, around the time that Etkin was joining the lab, Kandel published what could be considered a manifesto — “A new intellectual framework for

psychiatry” in the *American Journal of Psychiatry* — for today’s effort to infuse psychiatry with neuroscience. Kandel called for a new generation of neuroscientists to join with psychiatry to develop a neuropathology of mental illness, a change that seems to be well under way. “I used to get MD/PhD students going into neurology, but now they’re going into psychiatry,” Kandel says. Etkin was one of his earliest recruits. He had, in fact, planned on being a pediatric neurologist, but Kandel inspired his switch.

In 2002, when Etkin began working with fMRI, scientists were still figuring out how to image brain activity relating to anxiety and mood disorders. (The first fMRIs of humans were done in 1992.) The usual approach involves having study subjects inside the fMRI perform a particular task so scientists can determine how that particular stimulus changed activity in the brain. Earlier experiments had suggested that the amygdala, a pair of almond-sized bundles of nerve fibers in the middle of the brain, is activated when people are anxious. Etkin and his colleagues, though, believed the amygdala was only one part of the process. They wanted to document in greater detail how the brain regulates — without any conscious awareness — the emotional conflict underlying anxiety. In a nutshell, he wanted to answer this question: What is different in the brains of people who can implicitly regulate their feelings of anxiety as compared with those who cannot?

Etkin was looking for a task that would elicit the unconscious brain response to emotional conflict, and the solution arose as he was riding a bus across Manhattan to meet his wife. On the seat next to him was a colleague, Tobias Egner, PhD, who had been looking at means of testing in fMRI studies how the brain deals implicitly with cognitive (not emotional) conflicts. Egner, now an assistant professor in the psychology department at Duke University, told him of a classic technique for studying non-emotional

participants were shown two consecutive incongruent images, the response time typically improved. This demonstrates how the brain, without our being aware of it, is implicitly primed to resolve a cognitive conflict and thus gets faster at it.

Stroop-like effects occur in a multitude of common tasks. Take a car that’s skidding on ice. The initial reaction for those new to driving in winter is to steer the car in the opposite direction. It takes mental effort to do the right thing and to turn the car into the skid. After doing it once, however, there’s less hesitation about making such a move the next time.

Etkin and Egner, under the direction of senior scientists at Columbia, wondered if they could apply the Stroop paradigm to assessing emotional conflict.

Etkin selected facial expressions and typed the words “happy” and “fearful” on top of them. What happened when he used these in an fMRI study was more than what he and Egner had hoped for: After being shown two consecutive incongruent images, the participants, who did not suffer from a psychiatric disorder, activated a select part of the prefrontal cortex, never previously associated before with emotion regulation, and they reduced amygdala activity. In other words, the activity in these regions, as well as some other regions described in the study published in 2006, appeared to be responsible for the sort of implicit emotional regulation that prevents anxiety.

Further work was needed, however, to prove that the interplay among these regions is linked to anxiety. So after moving to Stanford, Etkin and colleagues extended his Stroop testing to people who met the diagnosis for generalized anxiety disorder. The results, published two years ago, were starkly different from those of the healthy participants. When shown consecutive incongruent images, the participants with GAD had little prefrontal cortex activity and no dampening of activity in the amygdala. Moreover, the GAD participants’

## Etkin selected

**FACIAL EXPRESSIONS AND TYPED THE WORDS ‘HAPPY’ AND ‘FEARFUL’ ON TOP OF THEM.**

conflict — the Stroop task — first identified in Germany in the late 1920s (and later made public in the United States by the psychologist John Ridley Stroop). It involves asking a participant to identify the ink color used on cards with two words “Red” and “Green.” Sometimes the color matches the word, sometimes it does not. What researchers established is that when forced to resolve a conflict — when the word and color don’t match, or are incongruent — study participants take longer to answer. Yet further research indicated that when

response time did not speed up when shown consecutive incongruent images.

“The robust group differences seen at both the behavioral and neural levels,” the researchers wrote, “suggest that the inability of patients to adapt to emotional conflict is an important aspect of the pathophysiology of generalized anxiety disorder — and potentially of other psychiatric disorders — and thus merits continued, deeper study.”

C O N T I N U E S O N P A G E 38



Neurologist and psychiatrist Mark George, MD, was studying brain imaging and depression in 1990 at London's Queen Square Hospital, a center for neurological diseases renowned for a century as a hotbed of discovery, when he bumped into a man in an elevator with an astonishing report. • "He said, 'You'll never believe it, but this person put a magnet to my head, and it made my thumb move,'" recalls George, who was fresh from South Carolina, where he'd just finished residencies in neurology and psychology. In fact, the man was part of a study in which researchers were experimenting with magnets to treat malfunctions of the brain's motor cortex — the part of the brain that controls voluntary move-

INSIDE THE HEAD :

The future of psychiatry

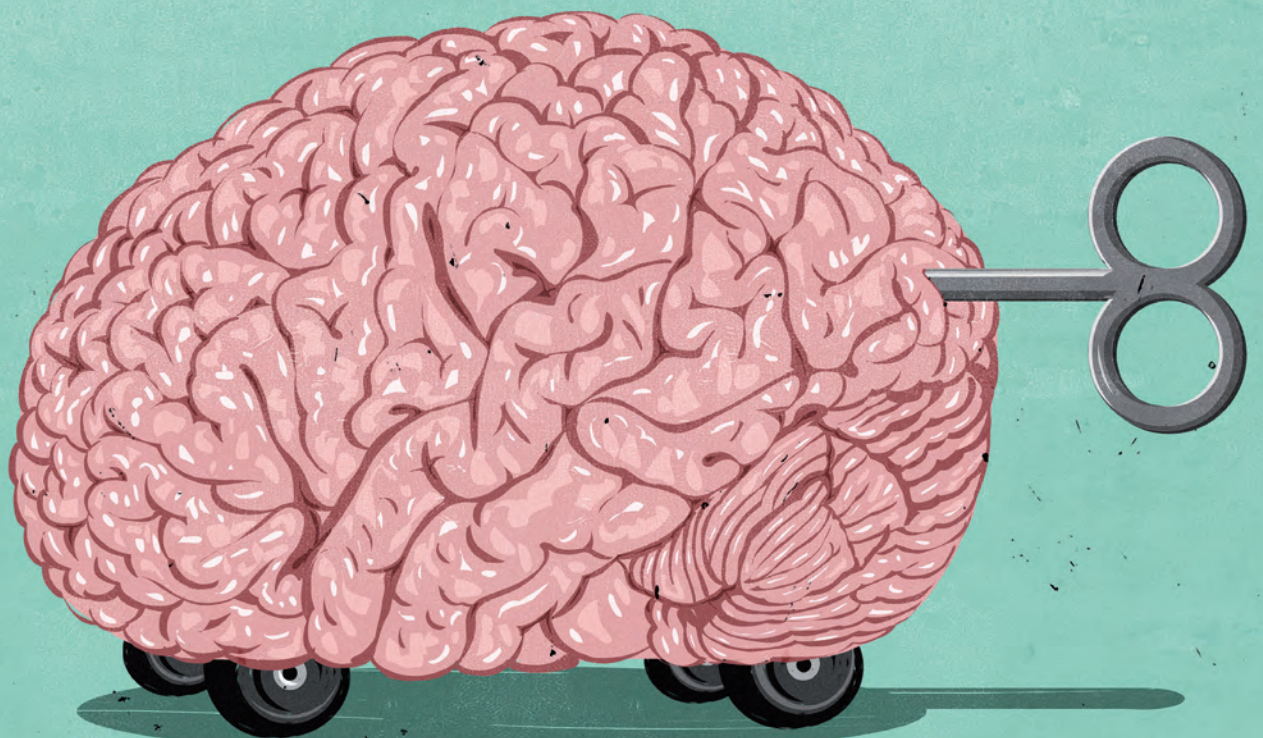
# POSITIVE CHARGE

NEW TECHNOLOGY TO TREAT DEPRESSION

By Ruthann Richter

ILLUSTRATION BY SHOUT

ments. • The encounter left George, then in his early 30s, with the "crazy idea" that it might be possible to use magnets to influence the brain in other ways and perhaps alter an individual's mood. After all, he thought, if a magnet could stimulate the brain enough to cause movement, might it be possible to position it over a spot where it might affect feelings and emotions? • Back in the United States, George took a research position at the National Institutes of Health and persuaded his boss to let him test the theory in healthy people, aiming magnets through their skulls to the area just behind their foreheads — the site of the prefrontal cortex, the brain's planning and decision-making center. Scientists





then were just learning about the brain's interconnectedness, so he speculated that in stimulating the cortex, he could reach deeper structures involved in depression and other mood disorders. It was a risky move, in that scientists were concerned that if magnets were powerful enough to move a thumb, they could be powerful enough to cause a seizure.

But, notes George, "It could be a window to the cortex and it could make people better." Now a professor of psychiatry, radiology and neuroscience at the Medical University of South Carolina, George became the first U.S. psychiatrist to use the technique, known as transcranial magnetic stimulation, to treat depression. About 3,000 patients received TMS in the past year, not including those in research studies, according to estimates from Neurostar, manufacturer of the only TMS device used for depression.

Psychiatrists are turning to TMS and other forms of brain stimulation as alternatives to drug treatment, which is often ineffective. Some 20 to 30 percent of people with severe depression fail to get relief from currently available medications; about 0.5 percent of adults in the United States suffer severe depression unaided.

"These patients can't work. They're not functioning. Their lives are pretty miserable," says Charles DeBattista, MD, professor of psychiatry and behavioral sciences at Stanford.

"It cuts across the economic spectrum," he adds. "We have former CEOs, doctors and university professors who become debilitated — they can't think or can't get out of bed. Sometimes they've lost the will to eat. I have seen patients wither away and die. So we need some options for those who don't respond to standard treatments."

Drugs, together with psychotherapy, have been the mainstay of treatment since the advent of the first antidepressants in the 1950s and 1960s, followed by the ever-popular SSRIs — medications like Prozac, Zoloft and Lexapro. But drugs are not foolproof, and some patients either don't respond or become resistant to them over time. Moreover, there are few new drugs in the pipeline, says Alan Schatzberg, MD, professor of psychiatry and behavioral sciences.

"It's relatively quiet, and that's unfortunate. Some companies are pulling out, and a lot of people are very worried about that," Schatzberg says. "Some people feel we need better animal models or a better sense of biology. We need to come up with innovative targets. The bottom line is companies are investing less, and we're looking at a potential shortage of new drug options over the next decade."

So attention has turned to such techniques as TMS and deep brain stimulation, which involves placing an electrode in deep brain structures and has long been used to reduce tremors and other symptoms of Parkinson's disease. Radiosurgery, used to treat tumors, is also being explored at

Stanford as a treatment for depression.

The stimulation methods rely on the brain's design as an exquisite piece of electrochemical machinery. When a nerve cell is exposed to electricity during normal function or as part of treatment, it opens its gates to a rush of ions, mostly sodium and calcium. This triggers an electrical impulse that travels down the length of the cell and activates connections with other cells.

With each movement or thought, that process is repeated thousands of times with neurons communicating via electrical signals in a complex system of circuitry. In depressed patients, the circuits involved in regulating mood don't function normally; connections are faulty or lost altogether. In theory, electrical stimulation may be able to jump-start the process and repair some of these broken circuits, thus relieving sufferers of their overwhelming despair. It would be something akin to rebooting an errant computer.

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### Electroshock and beyond

**T**he principle was first applied in the 1930s in the form of electroshock treatment, which delivers a jolt of electricity directly to the brain. The treatment, known today as electroconvulsive therapy or ECT, is used in 100,000 Americans annually and remains unquestionably the most effective therapy for major depression, freeing as many as 80 percent of patients from their symptoms. In the early days, however, it was crudely applied and subject to abuse, becoming the *bête noire* of the psychiatric field. Though it has evolved into a sophisticated therapy, with rigorous patient safeguards, it has never completely shed its early reputation (immortalized in the 1975 film *One Flew over the Cuckoo's Nest*). Moreover, the treatment can cause some disquieting side effects, including memory loss and effects on cognition. The fear of side effects and stigma around the treatment are a deterrent for some physicians and would-be patients.

"So there has been a major effort to develop therapies that can help people with treatment-resistant disease without significant side effects," says Brent Solvason, MD, PhD, medical director of psychiatric interventional therapy at Stanford.

In transcranial magnetic stimulation, a magnetic field passes unimpeded and uncharged through the skull, creating an electrical spark only when it bumps against neural tissues. As a result, the side effects — scalp discomfort, pain at the site and temporary headache — are minimal in comparison with ECT.

Amit Etkin, MD, PhD, a psychiatrist who comes to the field from the perspective of a neuroscientist, says he was drawn to TMS because he could apply it to manipulate small



sections of the brain and then use brain imaging technology to see the response. That makes it very useful for understanding brain networks, as well as for treating mood and anxiety disorders.

He sees TMS as the ultimate replacement for ECT, which distributes electricity widely through the brain, inducing a seizure in patients, and thus requiring anesthesia and muscle

relaxers. She learned about TMS from a friend and thought it was worth a try. She already had rejected ECT because of the possible cognitive side effects, including memory loss.

"I didn't feel I could afford to lose any more brainpower," she says, as there are days when her mind feels foggy. "So when I heard about this, I thought, 'Boy, this sounds really good.' There wasn't any radiation involved. It was pretty benign, and

## 'IT FEELS LIKE A WOODPECKER TAPPING ON THE SIDE

OF MY HEAD. IT DOESN'T HURT.

WHEN YOU GET USED TO IT, IT KIND OF FEELS GOOD.'

relaxers. TMS, on the other hand, precisely targets a specific area of about a square centimeter, or the size of a fingertip, Etkin says. The procedure is done without anesthesia, while the patient is fully awake.

The magnetic field quickly loses its potency, so it penetrates only a few centimeters into the skull. But because the brain is so interconnected, it can have an indirect impact on deeper structures like the amygdala, two almond-sized nerve bundles that process emotion, memory and fear.

"So you're stimulating one area, but it has wide effects," says Solvason, associate professor of psychiatry and behavioral sciences. Solvason, who has a background in cell and molecular biology, began experimenting with TMS in 1998 because existing treatments had been of little help to his patients, he says. He has used the technique in about 100 patients and, together with DeBattista, was involved in one of the TMS trials that led to Food and Drug Administration approval.

### One woman's experience

**L**ike many patients, Myrl, a 58-year-old Pacifica, Calif., resident, turned to TMS out of desperation. Haunted by depression for more than two decades, she had tried at least 10 different drugs, virtually everything on the market. Some gave her brief relief, in which she felt like a veil on the world had been lifted, and she could enjoy a simple walk outside. But then the curtain would fall again.

"It's paralyzing. There is no motivation there, even though I have lots of interests," she says. "And there is the isolation. Sometimes I find it hard to talk. Everything takes energy. It's just swimming upstream. Just getting up and taking a shower to get ready is overwhelming. I feel like I'm not really living — I'm just existing."

I was willing to try it because I had run out of other options."

At the Stanford Mood Disorders Clinic, Myrl, a spare, gray-haired woman in blue jeans, reclined in a light blue leather dentist's chair, hands resting on a magazine in her lap. DeBattista attached a 1-inch, T-shaped plastic strip to her forehead, which helped define the anatomy so he could properly position the magnet — heavy, figure-eight-shaped coils about the size of two fists. The insulated magnet has the strength of 1.5 Tesla, similar to those used in a standard MRI, and is placed against the left side of the head. A wire connects it to a computer, which DeBattista programmed to emit a series of pulses. Then the magnet began its rat-a-tat-tat, sounding like mini-jackhammer against the head without actually striking it.

"It feels like a woodpecker tapping on the side of my head," Myrl reported. "It doesn't hurt. When you get used to it, it kind of feels good."

Her forehead twitched with the pulsing of the magnet. Because of the muscle spasms, some patients complain of headache or pain at the site, but these typically resolve within a day, physicians say.

Myrl lay there calmly for the 37-minute session, submitting to the treatment without complaint. When she spoke, it was in a flat tone; her expression rarely changed. As she did crossword puzzles or tried to read her *Architectural Digest*, she received the standard 3,000 pulses, with short breaks in between. She returned daily for six weeks, as the therapy has to be repeated to achieve any long-lasting effect.

At the end of her sixth week, she noticed an improvement. Her husband told her she was joking and laughing more. And an incident with a family member that normally would have plunged her into depression has left her feeling unruffled. "There is definitely more resilience there," she says with a lift in her voice.

She's also begun thinking about returning to some creative hobbies she'd abandoned, like jewelry making and decorating. "I just feel excited about doing things that I'd put aside because I couldn't enjoy them like I once did."

The FDA approved the therapy in 2008 on the basis of a trial in 301 patients, including 30 at Stanford, who had tried all else and failed. Those patients who received TMS were twice as likely (24 percent versus 12 percent) to get better as those who got a sham treatment, in which a shield prevented the magnet from penetrating the brain. DeBattista says in daily clinical practice results are even better, with about half of patients responding. He notes clinic patients are typically on medication (not allowed during the controlled study), which might magnify the effects of TMS.

"Firing those neurons may help the medication work better," he says.

One of the limitations of TMS, which is available at most academic medical centers and some community hospitals, is its cost — \$8,000 to \$12,000 for a course of treatment — which is just beginning to be covered by insurance.

Moreover, the treatment is still very much evolving, as clinicians are trying to figure out which brain area to target for best results. Currently, they aim for the prefrontal cortex, as depressed patients appear to have reduced activity there, says Etkin, an assistant professor of psychiatry and behavioral sciences. But clinicians now use a very hit-or-miss approach to locate that spot, and about a third of the time, they miss, he says.

So Etkin has begun a study aimed at making the procedure more exact. For the study, patients lie in a standard MRI machine while undergoing TMS so Etkin and his colleagues can simultaneously expose the patients to TMS and obtain real-time data on what's happening in the brain. Stanford radiologists have created a special set-up for this purpose, one of the few in the country. This way they can see which regions of the brain are active during TMS and use that to develop new, more precise targets and, they hope, improve treatment results.

"One of the things that is shocking about the field is not only do we not know how to target it but we don't know how to personalize it," Etkin says. "We're really groping at straws in our current method, which I think will be revolutionized by the combined TMS/fMRI."

He also hopes the TMS/fMRI study will give clinicians a better understanding of the underlying mechanisms of TMS. Though it's believed to act on abnormal circuitry, either suppressing or stimulating activity there, it could in fact be working through an altogether different mechanism to relieve patient symptoms, he says.

Etkin is also testing the technique in patients with post-

traumatic stress disorder. He's enrolling 64 PTSD sufferers in a new trial in which he and his colleagues will map brain activity associated with psychotherapy treatment and with pre-treatment TMS stimulation in various areas in the prefrontal cortex. He and his colleagues then will look to see where brain activity in response to TMS matches brain activity associated with eventual response to psychotherapy. As with depression treatment, many PTSD patients are helped by psychotherapy — now the most effective treatment — but many are not, and in the case of PTSD, even fewer alternatives exist. "We can look at our scans subject by subject and see what's going on," he says. He hopes this work will form the basis for either a novel TMS treatment or a combined, new approach to PTSD, taking advantage of the strengths of both. At Stanford and other institutions, scientists are exploring TMS for treating other psychiatric disorders, including obsessive-compulsive disorder and schizophrenia, as well as non-psychiatric disorders, such as pain, Parkinson's disease, stroke and tinnitus.

#### Deeper treatment

**F**or depressed patients unreachable through TMS, Stanford investigators are looking at another option: deep brain stimulation. Jaimie Henderson, MD, associate professor of neurosurgery, has used DBS in some 600 patients with Parkinson's disease since 1996, when he was involved in the early trials. Now he's launching a study with Solvason and DeBattista, part of a multicenter trial in which they will test the stimulation technique in 10 patients with debilitating depression.

It is in many ways a last-resort option: "You don't get more invasive than opening up the skull and putting a probe in the brain," DeBattista notes. But if it works, it could be a godsend for those who are simply not able to function otherwise.

The approach is based on work by neurologist Helen Mayberg, MD, at Emory University, and neurosurgeon Andres Lozano, MD, PhD, at the University of Toronto, whose imaging studies showed that severely depressed patients had hyperactivity in a region of the cortex known as the subgenual cingulate, also called Brodmann Area 25. This thumb-nail-sized structure, labeled in 1909 by German neurologist Korbinian Brodmann (who first conceived the idea of mapping and numbering sections of the brain), is a bit like the brain's Grand Central station, connecting networks involved in mood, anxiety, memory and cognition.

In 2005, Mayberg and Lozano began zeroing in on that target, implanting electrodes in five patients. Later they expanded their testing to 20 patients, with 60 percent of them

responding gradually over six months. Some of the results were striking, with patients doing so well that they were able to return to work and re-engage in family and social activities.

"Patients described it like the release of a block, the removal of a veil," Henderson says. "Colors seem brighter. Things seem more interesting. This all-encompassing feeling of despair is relieved."

In the Stanford trial, he will implant two electrodes into the target area, one on each side, then connect these by wire to a battery pack buried in the patient's chest wall. Patients will be able to turn the device on and off, making the treatment reversible.

"I'm optimistic," DeBattista says. But, he notes, "It would be nice to have something less invasive. If we have a target, we might be able to get to that target without opening up someone's skull."

That's the goal of another small study at Stanford using the Cyberknife, a noninvasive form of precision radiotherapy used for more than a decade in cancer patients. The therapy, invented by Stanford neurosurgeon John Adler, MD, uses high-dose precision radiation on a particular target with sub-millimeter accuracy without harming nearby cells.

Since the spring of 2010, he and Solvason have treated three severely depressed patients with the Cyberknife in a safety trial, using it to slow down areas of the brain that are too active in the depressed state. Like the deep brain stimulation trial, this one targets Brodmann 25.

One of the challenges is finding the right radiation dose to disable the cells, but not kill them, while maintaining a sustained antidepressant effect, Solvason says.

Yet another option for those resistant to standard therapy is vagus nerve stimulation, in which clinicians install a stimulator in the armpit and snake the wire to one of the vagus nerves, a major pair of nerves that run from the

brainstem through the neck and down to each side of the chest and abdomen. These nerves carry messages between the body's major organs and areas of the brain that control mood, sleep and other functions. The stimulator is programmed to send out signals along the nerve, in the form of short bursts of energy, to the brain's mood centers to help relieve depression symptoms.

The FDA-approved technique is commonly used in pa-

tients with epilepsy, and has been found to be moderately effective in patients with intractable depression, says John Barry, MD, a professor of psychiatry and behavioral science who was involved in a major trial on the treatment. But he says the therapy hasn't caught on in the psychiatric community, in part because of its high cost — more than \$33,000 for the device alone, not including implantation — which is not typically covered by insurance.

"It's probably useful, but I don't think it's found its place yet," Barry says.

Scientists say these techniques still need refinement before they can be counted on for wider use.

"We have a lot to learn," DeBattista says. "We don't know what will work in the long term. We have a lot of brave patients who are desperate and for whom there are no alternatives."

Etkin says he envisions a time when these patients, rather than spending years on

a hopeless quest of drug after drug, would be referred early on to a specialty TMS diagnosis and treatment center where they would undergo brain imaging and receive a tailored, personalized treatment using one or multiple magnets simultaneously targeting superficial structures in the cortex, as well as deep brain structures. Treatment times would be reduced and side effects minimal. "That would certainly be a triumph for neuroscience in the clinic," he says. **SM**

Contact Ruthann Richter at [richter1@stanford.edu](mailto:richter1@stanford.edu)

## AT A GLANCE

### BRAIN STIMULATION FOR MENTAL ILLNESS

#### ELECTROCONVULSIVE THERAPY

The first form of electrical brain stimulation used in medicine, it is applied today in some 100,000 Americans each year for treatment of major depression.

#### TRANSCRANIAL MAGNETIC STIMULATION

Approved by the federal Food and Drug Administration in 2008 for treatment of major depression, it is emerging as a new technology for treating depression and other disorders.

#### DEEP BRAIN STIMULATION

First approved by the FDA in 1997 for treatment of movement disorders, including Parkinson's disease. It is currently being used experimentally at Stanford and elsewhere as a treatment for major depression.

#### VAGUS NERVE STIMULATION

FDA-approved in 1997 for the treatment of epilepsy. It was also approved in 2005 for treating major depression, though is not widely used for this purpose.

#### CYBERKNIFE

Commonly used as a cancer treatment since its FDA approval in 1999, it is now being tested at Stanford in a small group of patients to treat major depression.





Janet Cartwright starts her stopwatch. The video playing in front of her shows an 11-year-old doing homework. Like other children with autism, Katie Halpin, the girl in the video, struggles to maintain self-control, sometimes talking, yelling or thrashing around. Cartwright sits with a tidy graph-paper grid in front of her, charting Katie's behaviors in 30-second intervals for the entire half-hour video. • It is a standard scene from psychological research, with one important difference: Cartwright is not a research profes-

sional. The Santa Cruz, Calif., lawyer is Katie's mother. • Parent involvement is widely recognized as critical for effective autism treatment, and many intervention programs already incorporate a parent training component. Cartwright's foray into science is the product of a new effort by clinician-scientists at Lucile Packard Children's Hospital and the School of Medicine to broaden that involvement in light of the increased demands for services and limited resources. • Three programs, involving only about 100 families so far, offer a way out of the bind parents of autis-





INSIDE THE HEAD:

The future of psychiatry

# autism

ANSWERS

Parents  
run  
experiments  
to see what works

BY ERIN DIGITALE

Photography by Brian Smale

At left: Janet Cartwright and her daughter, Katie Halpin. Cartwright used a scientific method to study Katie's homework habits.

tic children find themselves in — they want to help their children but don't know how, and medical experts have no ready answers either. One program makes therapy training sessions more accessible by teaching parents in groups. Another program, which Cartwright took part in, teaches parents how to critically evaluate autism treatments; how to, in effect, run miniature scientific studies on their own children. A third small program teaches parents socially based interventions based on a model developed by the Pacific Autism Center for Education in San Jose.

“Raising a child with autism is very stressful for families,” says Grace Gengoux, PhD, a Packard Children's psychologist and clinical instructor in psychiatry and behavioral sciences at Stanford who teaches the therapies. It's difficult enough to handle the core features of autism — impaired language development, poor social interaction and repetitive behaviors. But the responsibility to direct the child's treatment can be overwhelming. It's not uncommon for families to try a dozen or more therapies, which can range from well-studied options such as speech and behavioral therapies to treatments that

have never been scientifically tested, such as vitamin supplements or chiropractic adjustment.

Giving parents well-researched therapies to tailor to their own kids, as well as a method for making decisions about which autism therapies to pursue, can simultaneously advance the child's treatment and reduce parents' stress.

Strong involvement from parents is more important than ever. Next year's revisions of the "bible of psychiatry," the *Diagnostic and Statistical Manual of Mental Disorders*, may tighten criteria for milder diagnoses on the autism spectrum and exclude some kids from formal autism-spectrum diagnoses. If that happens, children may not qualify for therapies now covered by their health insurance and state agencies. "Parents might be more willing to learn these interventions and implement them at home," says Antonio Hardan, MD, a Stanford professor of psychiatry and behavioral sciences who treats autism at Packard Children's.

### TURNING PARENTS INTO THERAPISTS

One reason raising a child with autism is so stressful is that instinct can fail you. Other parents rely on gut feelings, childhood memories and advice from relatives and friends. But if your child has autism, it's not so easy.

"The things we're teaching parents to do are quite different from what a normal attentive parent would do," says Gengoux.

For instance, one therapy Gengoux teaches, pivotal response training, includes exaggerated positive consequences when the child attempts to use language. To conduct the therapy, parents pick something their child cares about and then try to engage the child in conversation about it. If the child makes even the smallest effort to converse, parents respond with lots of praise and with rewards relating to what the child said.

For instance, one boy Gengoux helped treat had never talked to others, yet occasionally said a word or two to himself. "I sat down with his mother and said, 'OK, we ought to be able to capitalize on this,'" Gengoux says. The boy adored bicycles and would sometimes say "bike," so they took him to a spot on campus with lots of bicycles and waited until he used the word. "We gave such positive reinforcement by praising him and letting him run over and touch the bikes that he began to understand the benefits of using words and was able to start communicating," Gengoux says. "He's now a kid who talks a ton."

The Packard Children's team is studying efforts to train groups of parents to deliver PRT — an unusual format for such training, but one with potential advantages. It's more efficient than one-on-one PRT lessons and gives parents the chance to learn from each other.

The team's first scientific paper on the training, published in 2010, showed encouraging results. Using before-and-after videos of parents' interactions with their kids, the scientists counted how many times children spoke and scored parents' ability to follow PRT protocols. After parents participated in a 10-week PRT training group, their "treatment fidelity" scores more than doubled, and the children's average number of "functional utterances" increased from 27 to 42 per 10-minute interval.

Though these results are heartening, the researchers recognize that asking parents to deliver treatment has its limits. Parent-delivered therapy is intended to supplement, not replace, autism treatment delivered by professionals, they're quick to emphasize. And having Mom or Dad give treatment won't work for every family.

"Just like not all of us could be physicists, not all of us could be therapists," Hardan says. The family's schedule, parents' level of education and parents' cognitive traits are all factors that Hardan speculates could influence their success.

"For instance, there is clear evidence that aspects of the cognitive traits associated with autism are inherited, which could mean that some parents will struggle to deliver therapy," he says.

For Hardan, seeing parents' efforts toward their children — even in the face of daunting obstacles — is a strong motivator to continue his autism research.

"These parents are so committed to their kids, to doing their best to make their children function better," he says. "You can't but go out of your way to help them out."

### TURNING PARENTS INTO SCIENTISTS

Whether they're up to it or not, all autism parents face the challenge of deciding which treatments their child should receive. Although a child's physicians, teachers and therapists weigh in on this question, the decision-making power rests with parents.

"One of the biggest questions I get is, 'What do you think about this treatment?'" says Kari Berquist, PhD, who developed Packard Children's treatment-evaluation group for parents after studying the effectiveness of a similar program for her dissertation at Claremont Graduate University. "Often I have to say, 'I'm not sure; I haven't heard of that.'" But lack of scientific support often doesn't deter parents eager — or desperate — for new ways to help their kids.

"It's easy to get wrapped up in the fear of the diagnosis and fear of what the future holds," Cartwright says. Research demonstrating the benefits of early, intense autism interventions has led to more autism services, but has also fed parents' anxiety about treatment.

"Parents are pouring all this money, hope and desire into these interventions, but then they're kind of getting stuck," says



Berquist, who completed a psychology fellowship at Stanford before joining the faculty as a clinical instructor in 2011. The trouble with an “everything and the kitchen sink” approach to selecting autism treatments is that it carries constant risks of physical, financial, mental and emotional exhaustion.

To help parents out of this rut, Berquist decided to turn them into scientists. The 12-week educational program she designed brings together groups of parents to learn the psy-

chology of human decision-making and the rudiments of single-subject study design. Parents can use her techniques to evaluate any autism therapy their child undergoes; she’s seen families apply her methods to test the effectiveness of everything from behavioral treatments and school-based academic tutoring to equestrian therapy and vitamin B12 supplements.

The point is to help parents make rational decisions about starting and continuing autism treatments, and to learn to identify when curtailing a therapy is a step forward.



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The point is to help parents make rational decisions about starting and continuing autism treatments, and to learn to identify when curtailing a therapy is a step forward.

### THE TROUBLE WITH SPEECH CLASS

Sitting in a Palo Alto café, Cartwright pulls out a thick binder and the green pencil case that holds her stopwatch, mechanical counter and pencils: her equipment for the transition from mom to scientist. Her eyes light up as she describes a mystery that Berquist’s class helped her solve.

In spite of her autism, “Katie is a really friendly, inquisi-

“I started pinpointing the antecedent,” Cartwright says. Following Berquist’s instructions to collect all the details she could find, she learned that each speech session caused Katie to miss portions of classes on her best subjects. Depending on the day, the speech session might overlap with art, PE, folk dance, social studies or music.

A typically developing 11-year-old would have come home from school and said, “Mom, I hate not finishing my art projects. I don’t like arriving in the middle of music and not knowing the words.” Katie didn’t say any of that.

“She wants to be compliant,” Cartwright says. “Nobody told me until I investigated.”

Cartwright performed a detailed cost-benefit analysis she learned in Berquist’s class. Not only was Katie missing activities she liked, Cartwright realized, she was also missing opportunities to practice conversational speech and social behavior. Because Katie already received speech therapy

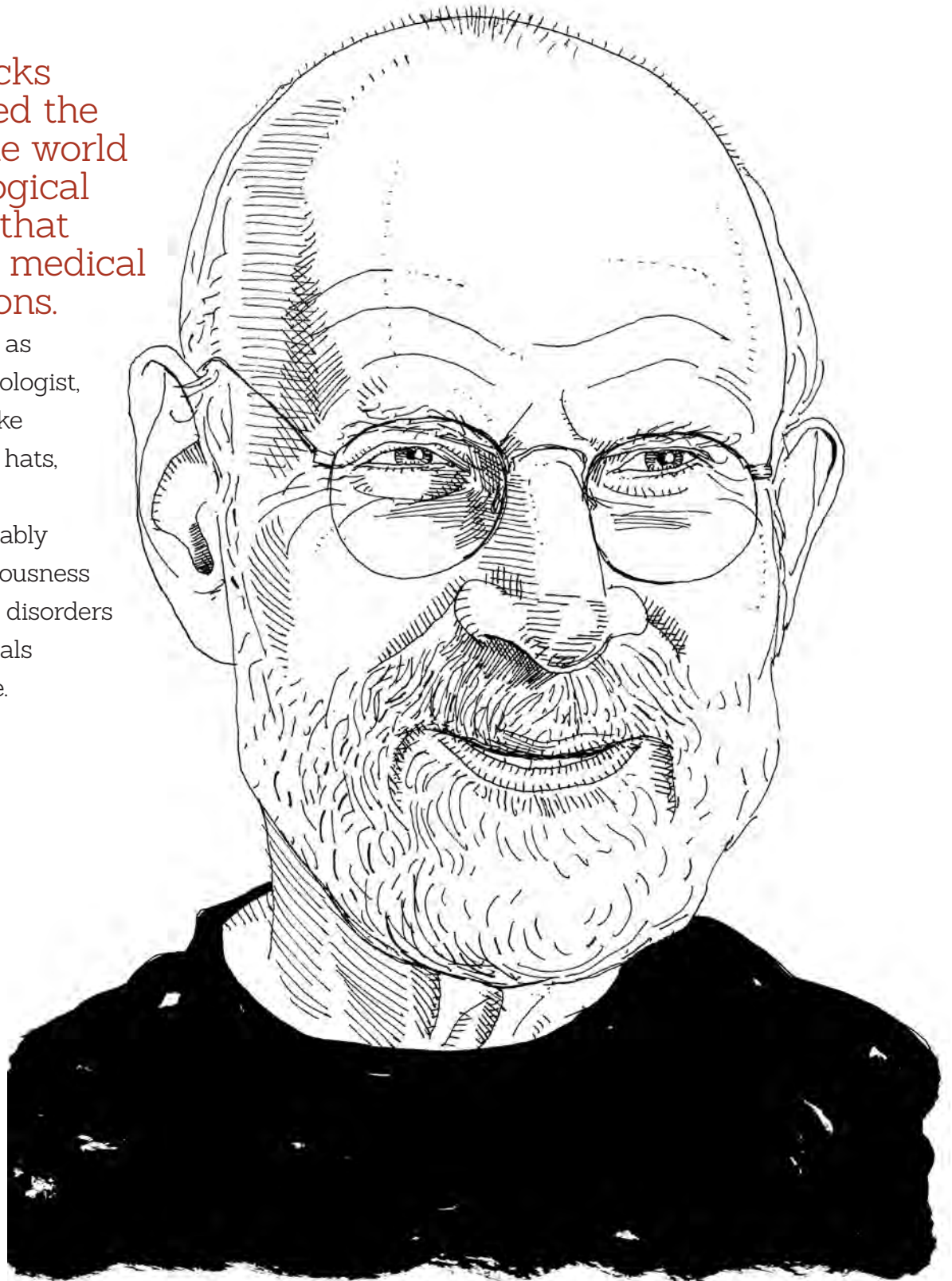
C O N T I N U E S O N P A G E 4 0

# Sleuth of the

A CONVERSATION WITH OLIVER SACKS

Oliver Sacks  
has opened the  
eyes of the world  
to neurological  
maladies that  
defy easy medical  
explanations.

In his practice as  
a general neurologist,  
patients mistake  
their wives for hats,  
long-dormant  
minds inexplicably  
recover consciousness  
and rare brain disorders  
afflict individuals  
out of nowhere.





# mind

INSIDE THE HEAD:  
The future of psychiatry

IN HIS LATEST BOOK, *The Mind's Eye*, Sacks writes of a variety of visual abnormalities that stem from neurological accidents. Besides detailing the unusual nature of these disorders, Sacks unveils the miraculous ways that human beings often adapt and compensate for their illness. He also writes of confronting his own neurological malady, a condition known as prosopagnosia or face blindness. And he describes how he has coped since experiencing a radical change in his vision seven years ago.

Diagnosed with ocular melanoma in 2005, Sacks has lost vision in his right eye along with the ability to see in three dimensions, a sad irony for someone who has long been a member of the New York Stereoscopic Society. He works surrounded by blown-up copies of documents and magnifying glasses, putting the final touches on his next book, which will be about hallucinations. The Columbia University Medical Center physician continues to see patients and still swims every day. He spoke with Paul Costello, chief communications officer for the School of Medicine, who gets the sense from talking with him that he's always swimming upstream.

**COSTELLO** In *The Mind's Eye*, people surmount incredible challenges: an art dealer whose strokes leave her without language but is still able to communicate, a novelist who loses his ability to read but not to write. They seem almost superhuman, with great courage and unusual perceptual skills. Does coping with neurological problems hone survival instincts?

**SACKS** Well, it can. I think any disadvantage can. What do they say, what doesn't kill one strengthens one? But I may be guilty of some selection in writing about people who have one way or another dealt with or transcended their conditions, rather than being beaten down by them. Obviously, in real life, one sees both.

**COSTELLO** The people you write about compensate in many ways. What do we know about the biological basis of compensation?

**SACKS** Living organisms will find ways of accommodating to adverse circumstances. With bacteria, it's sort of genetic. In a few

generations, you'll find bacteria that can get nourished by an antibiotic that would have killed them 20 generations earlier. But in the individual, there's this tremendous power to go on regardless, even if you break a leg on a mountain and no one else is there.

But in particular, the brain is enormously resourceful and has all sorts of tricks up its sleeve. For example, the Canadian novelist who became unable to read: He started to read again and wondered if his brain was healing. It turned out he was still visually totally unable to read, but unconsciously he had started to move a finger and then his tongue [on the roof of his mouth], copying what he read. Since, in this condition, one can write even though one can't read, he was in effect reading by writing with his tongue. That sounds weird and wild, but...

**COSTELLO** It does. It sounds so wild.

**SACKS** But it worked. There was one point at which he bit his tongue and it got sore and swollen and he said he couldn't read for two weeks because of his tongue.

**COSTELLO** Would you talk more about the plasticity of the brain?

**SACKS** First, one needs to say that the brain and nervous system in general has more ability to recover and even generate new nerve cells than some of us realized. But also there's this capacity to develop new paths in the existing machinery. I encourage patients to explore this and to try to do things a different way — although, they often discover this for themselves. I will say to patients, "I'm not sure that I can cure you or I can help this directly. But let's think about other ways of living, other ways of doing things, and think positive."

**COSTELLO** When you lost vision in your eye, you began having hallucinations. Do you still have them?

**SACKS** Oh, I do. If I sit here and look up at the ceiling, it is covered with what look like runes or hieroglyphics. They vaguely resemble English letters or numbers or Greek letters. But I'm used to that, as I'm used to my tinnitus hissing in my ears, and I pay no attention to it.

**COSTELLO** I read that your vision loss also led to a loss of stereovision. How are you

coping with everything looking two-dimensional instead of 3D now?

**SACKS** I was rather dangerous pouring wine or tea for some people because I would miss the glass and pour it into their lap. Sometimes, when shaking hands, my hand would miss their hand by a foot or so. I think I've become more skillful at making judgments with one eye. I mean, people who lose an eye early can become ball players and aviators. In one's late 70s, you don't adapt so easily. I've had particular dangers going down stairs, and I will hold a rail or I will count, I will feel for the next step with my toe. But even so, I may have an overwhelming sense that there isn't another step, so I have to learn to disbelieve my eyes.

**COSTELLO** You also write about your face blindness. How did you come to realize that was a disorder?

**SACKS** I don't think that was until I was an adult and met my brother in Australia whom I hadn't seen for 35 years. He was also quite unable to recognize faces, including his own, and places. Then, after I published *The Man Who Mistook His Wife for a Hat*, I got many, many letters from people saying they'd had this sort of thing all their lives and it was often in the family. At that point I realized that this must be something quite common, but almost never discussed. I think one of my reasons for writing is to open up a subject so it can be discussed.

**COSTELLO** When I read reviews of your new book, critics wrote first and foremost about survival and compensation and less so about the individual disorders. Is facing adversity what you want people to focus on?

**SACKS** Well, yes, I think survival is my theme, but I can only explore the theme in a highly specific way. I think both impulses are there. There's a great physician, William Osler, who once said, "To talk of diseases is a sort of *Arabian Nights* entertainment," which sounds like a hideous thing to say. But there is something very interesting about what happens to people, and that's also very frightening. It's also inspiring to know how people deal with it.

*This interview was condensed and edited by Rosanne Spector.*

WEB EXTRA HEAR THE INTERVIEW AT [STANMED.STANFORD.EDU/2012SPRING](http://STANMED.STANFORD.EDU/2012SPRING)



# THE NEUROS

IN THE PAST 10 OR 15 YEARS, there's been a shift in thinking about addiction, to a new appreciation that it is, at its root, a maladaptive form of learning. And like learning to ride a bike, addiction is not quickly unlearned. • If you think quitting is a simple matter of willpower, you're in good company. More than a third of the general public agrees, according to a 2008 survey by the federal Substance Abuse and Mental Health Services Administration. But it's tougher than that.

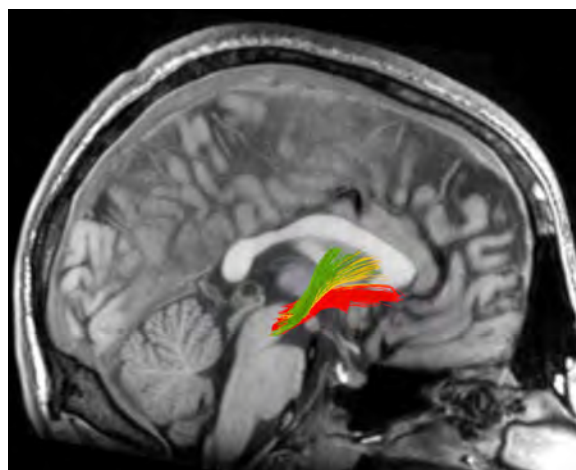
"It's kind of like putting on a lot of weight," says Keith Humphreys, PhD, a Stanford professor of psychiatry and behavioral sciences who has served as a senior White House drug-policy advisor. "Your body changes, and from then on losing weight is way harder than it ever was before you got fat in the first place. Because addiction-associated brain changes are so enduring, a lot of people are going to relapse. So the course of treatment has got to be longer-term than it often is."

Some of the key biological insights were made by Stanford neuroscientist Rob Malenka, MD, PhD, who continues his studies using animal models to extrapolate to humans. And now others, like brain imaging expert Sam McClure, PhD, are finding that changes Malenka sees in rats take place in humans as well.

This new understanding of addiction's long-term grip has policy implications: A short-term detox stint to rid the body of the unwanted chemical just won't cut it. Authorities have to be prepared to treat addiction as they would any chronic disease, even though that implies long-haul and therefore costlier treatment (it's still a lot cheaper than imprisonment). An equally important implication: They must also try their best — from both health and cost standpoints — to prevent people from starting down that lonely, dangerous road in the first place.

## Unforgettable

THERE ARE THINGS YOU DON'T FORGET, AND THERE ARE THINGS YOU CAN'T. For people who become drug addicts, the drug experience — the substance, but the entire "scene" too — is not only unforgettable but indelibly etched into the physiological brain circuitry that drives us onward through the obstacle course of existence.



In this MRI of a brain (side view), the green, yellow and red areas indicate bundles of neurons involved in addiction. Red represents reward pathways; green and yellow signify habitual responses.

# SCIENCE OF NEED

## Understanding the addicted mind

By Bruce Goldman

PHOTOGRAPHS BY KELLY HENNIGAN

And much of that memory is false. Because all addictive drugs appear to share a rather mysterious property: They're "better than the real thing." Better, that is, than the real things our reward circuitry was designed by evolution to reward: food, sleep, sex, friendship, novelty, etc. And better, even, than they were the last time around. At least, it sure seems that way to the addict.

About 25 million Americans are addicted to drugs (including alcohol but excluding nicotine), about the same number as those who have diabetes. But wanting a drug — really, seriously craving it — doesn't mean you have to like it. "That's a big part of the problem of addiction," says Malenka, the Nancy Friend Pritzker Pro-

fessor in the Department of Psychiatry and Behavioral Sciences. Malenka was among the first investigators to home in on the molecular details of just how the mechanisms involved in memory and learning are hijacked by drugs of abuse.

Addictive drugs mimic natural rewards such as food and sex by kindling a network of brain areas collectively called the reward circuitry, which is responsible for enjoyment — which if you think about it, is an important survival response. It gets us to do more of the kinds of things that keep us alive and lead to our having more offspring: food-seeking and ingestion, hunting and hoarding, selecting a mate and actually mating.

Moreover, addictive drugs fire up the reward circuitry in a way that natural rewards can't — by, in a sense, pressing a heavy thumb down on the scale of pleasure. Over time, the desire for the drug becomes more important than the pleasure the addict gets from it. By the time the thrill is gone, long-lasting changes may have occurred within key regions of the brain.

The brain is a little bit like the big snarl of tangled wires snaking their way out of that six-outlet surge protector behind your bed. They know where they're going, even if you don't. Nerve cells (or neurons, as scientists call them) can be seen as hollow wires transmitting electrical currents down long cables called axons to other neurons.

Addiction was once defined in terms of physical symptoms of withdrawal, such as nausea and cramps in the case of heroin or *delirium tremens* in the case of alcohol, which reflect physiological changes within cells of an addict's body. It's now seen as changes in brain circuits, or combinations of neurons; in other words, the very neurophysiological changes that result from learning and experience. You crave, seek and use a pernicious drug again and again because you have a memory of it being more wonderful than anything else, and because your brain has been rewired so that, when exposed to anything that reminds you of the drug, you will feel rotten if you don't get some.

"These are symptoms of a brain disease, not a mere weakness of will," Malenka says. He and other researchers are working to understand addiction as a sum of behavioral consequences of changes within nerve cells that occur with repeated drug use. Over time, these subcellular changes alter the strength of connections in the circuit, essentially hardwiring the yen for drugs into a habitual craving that is easily reignited not only by the drugs but also by environmental cues — people, places, things and situations associated with past drug use — even when the addict hasn't been anywhere near the drug or the drug scene for months or years.

#### Serendipity strikes

IN THE 1950S JAMES OLDS, PHD, A POSTDOCTORAL RESEARCHER WORKING WITH PSYCHOLOGIST Peter Milner, PhD, at McGill University in Montreal, was conducting experiments to try to assemble a wiring diagram for some of this complicated brain circuitry. They were using a then-new

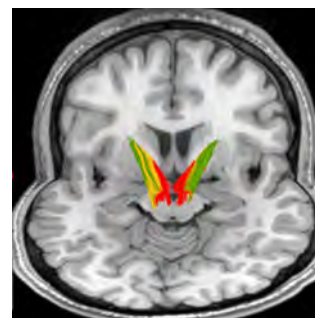
technique, based on the understanding that neurons are at heart electrical critters, that came down to sticking electrodes (painlessly) into a rat's brain, running an electric current and seeing what happened.

At one point Olds and Milner were shooting for an area of the brain called the reticular formation, an archipelago of interconnected clusters dispersed throughout the brain and involved in arousal and attention. But they missed and hit another circuit by accident. They discovered that when they stimulated this circuit, the animals loved it.

So the investigators tried something new. They taught the rats to press a lever in order to deliver shocks to their own brains, and recorded the points in the brain that rats liked to electrically stimulate over and over again by pressing that lever — and press it they would, sometimes for hours on end, to the exclusion of just about anything including eating or drinking. (Of course, the rats couldn't move the electrodes from one part of their brain to another. So Olds and Milner did that for them.)

Point by point, Olds and Milner were able to map the network of brain regions, interconnected as they are by bundles of axons running from one region to the next, that became known as the reward circuit. To oversimplify things a great deal, this circuit includes nerve bundles that run from deep inside the brain to spots such as the nucleus accumbens (associated with pleasure), the more recently evolved prefrontal cortex (involved in decision-making, planning and so forth), and other places of more ancient evolutionary vintage that control habitual movements and are sometimes referred to as the "lizard brain."

But what flips on the reward circuit in regular life, when electrical zaps to the brain are blessedly few and far between? The same chemical that's triggered by dope. It's called dopamine.



A brain, viewed from behind in two planes, showing the pathways implicated in addiction. The pathway travels from dopamine neurons (central) to areas in the striatum.

**YOUR BRAIN HAS BEEN REWIRED SO THAT,  
WHEN EXPOSED TO ANYTHING THAT REMINDS**



## Dope fires up your dopamine

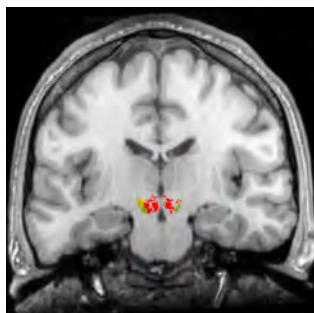
DOPAMINE IS ONE OF A GROWING NUMBER OF KNOWN NEUROTRANSMITTERS, substances neurons produce for the purpose of relaying information from one neuron to the next. Different groups of neurons manufacture different neurotransmitters, which all work pretty much the same way but in different nerve bundles and with a spectrum of different results. These substances are stored inside numerous tiny bulbs budding from points along a neuron's long, electricity-conducting axon at key contact points the neuron shares with other neurons.

When an electrical signal roaring down the axon's surface rumbles past one of these little bulbs, myriad molecules of neurotransmitters get squirted into the surrounding space. They diffuse across that space (called a synapse) to specialized receptors on the abutting neuron, where the interaction can either set off (enhance) or shut down (impede) a new electrical current in the downstream neuron.

These dopamine-squirting neurons constitute a tiny fraction of all neurons. But each of them can network with up to 10,000 or more other neurons stretching to the far corners of the brain. A dollop of dopamine in your tank can really boost your reward mileage, so to speak.

Once dopamine's centrality to the neurons constituting the reward circuit was worked out, people started wondering whether drugs might activate the reward circuits. It turned out that they do.

"One reason that the advances in our study of the neurophysiology of addiction so far exceed our understanding of other psychiatric disorders is because the animal models for addiction are extremely good," says Malenka. Teach a rat to press a lever for an infusion of a drug of abuse, and you will see the same compulsive behavior in the rat that you would in a person. "A rat will work very hard to get drugs," he says. "It will press that lever hundreds, even thousands, of times and endure pain and suffering to get drugs."



In this rear view of the brain, the colored areas show the origin of the dopamine neurons in the midbrain.

As these animal studies have shown, virtually all abused drugs — for instance, heroin and other opiates; cocaine, amphetamines and other psychostimulants; nicotine; and alcohol — operate by interfering with the reward circuitry. They cause the release of dopamine in target structures such as the nucleus accumbens, that key structure in the experience of pleasure.

Different drugs do this in different ways. Cocaine and amphetamines prolong the effect of dopamine on its target neurons. Heroin inhibits other neurons that inhibit these dopamine neurons. (In the logic circuitry that is the brain, a double negative roughly equals a positive.)

## Hijacking the reward system

YOU MIGHT THINK THAT THE MORE YOU EAT, OR THE MORE SEX YOU HAVE, or the more good vibrations you get, the more dopamine your reward-circuit neurons will squirt at their target structures in the brain. But it's not so simple.

A seminal 1997 *Science* paper by P. Read Montague, PhD, at Baylor postulated that what really gets the reward circuitry jazzed up isn't so much the good vibes as it is the extent to which the goodness of the vibes exceed expectations.

The newer theory was based on animal studies involving lever pressing, with a twist. In this case, the test animal learns that if it presses a lever after it receives an environmental cue — to wit, a light goes on — it will get a reward: say, a nice slice of apple or a drop of juice, both of which rats love. Of course, the animal soon learns to reach for the lever the instant the light goes on. With repeated exposure, the rat gets the hang of it, and a few interesting things happen inside its brain. First of all, the reward itself (the food) no longer produces the dopamine surge associated with reward-circuit activation.

Second of all, it is now the light, not the food, that triggers the activity in the reward circuit. The timing of the reward-circuitry's dopamine squirts has shifted from the time of reward delivery to the time of the cue (the essence of the so-called "conditioned response" familiar to anyone who has ever taken Psychology 101).

It's not that the juice or apple slice no longer tastes good. It's that the reward circuitry is responding to the difference between what we expect and what we get. How much dopamine gets secreted depends not on how great the reward is,

C O N T I N U E S O N P A G E 4 0

YOU OF THE DRUG, YOU WILL FEEL  
ROTTEN IF YOU **DON'T** GET SOME.

# hit

## RECORD

CONDUCTING FIELD RESEARCH — LITERALLY —

TO EXPLAIN CONCUSSIONS

**On Oct. 5, 1996, Stanford faced University of Washington on the gridiron at Husky Stadium in Seattle.**

**Toward the end of the first half, Cardinal quarterback Chad Hutchinson threw a short pass.**

**A second later, a defensive back for the Huskies plowed into his chin, helmet-first, and another defender drove him to the ground.**

**“That old turf up at Washington was hard,” Hutchinson recalls. •**

**He picked himself up and walked a few steps before stumbling into a teammate.**

**There was blood on his jersey. Something else was wrong too.**

**“I felt like I was drunk. I was in a fog,” he says. •**

**A doctor checked him on the sidelines.**

**“I was coherent enough to answer his questions correctly,”**

**says Hutchinson. He was subsequently allowed to return to the game. •**

LUCKILY, HUTCHINSON SAYS, IT WAS THE FIRST AND LAST CONCUSSION OF HIS CAREER. Today, however, it's doubtful he would have been permitted to stay in the game; he was at risk for second-impact syndrome, a catastrophic swelling of the brain that can occur if another concussion is sustained shortly after the first one. • Fifteen years ago, concussions, while not treated lightly, did not inspire the kind of worry they do now. That sports-related brain injuries have since become a focus of national concern is largely due to reporting by *The New York Times*' Alan Schwarz, who in 2007 began writing about how scientists had linked concussions, as well as recurrent sub-concussions, to long-term cognitive problems such as depression and early onset dementia in current and retired professional football players. “Sub-concussion” is the somewhat nebulous term for a violent head impact that doesn't cause a concussion, and generally goes unnoticed by players, but that many scientists believe cumulatively can have serious, long-term consequences for cognitive health. • Over the past dozen years, a steady drumbeat of research has correlated concussions with chronic neurologic problems. A 2000 survey of 1,090 retired National Football League players found that those who had suffered at least one concussion during their careers reported more speech difficulties, confusion, headaches and trouble recalling recent events, among other neurologic problems, than those who had not. A 2007 study of 2,552 retired professional players found that those who reported having had three or more concussions were three times more likely to be diagnosed with depression than those with no history of concussion. • Yet even though concussions, also called mild traumatic brain injuries, are commonplace, little is known about them. This is where Stanford's Dan Garza, MD, comes in. The emergency and sports medicine physician has launched an ambitious study of the mysterious affliction. • Last fall, when I went to visit Garza at his office, in the Lacob Family Sports Medicine and Human Performance Center at Stanford, he took me to the human performance lab, where a dummy head wearing a football helmet was attached to a cable-and-pulley contraption. On closer inspection, you could see that the head also had a mouth guard, the kind used by athletes in contact sports to protect their teeth. But it was no ordinary mouth guard; it

By JOHN SANFORD

ILLUSTRATION BY DAVID PLUNKERT





Plunkert



contained tiny accelerometers and gyroscopes. James Mattson, Garza's research assistant, pulled a cord, and the head fell about 3 feet, coming to a stop with a crash.

"We've dropped the head probably a few thousand times from various angles," says Mattson, a Stanford graduate in human biology. The purpose was to confirm that the mouth guard would accurately measure the force experienced at the center of a football player's head when jolted by a collision — either with another player or the ground.

"We discovered that the device measures impacts very, very accurately," says Garza, who last season equipped two dozen members of the Stanford University football team with the high-tech mouth guards, manufactured by the Seattle-based company X2 Impact.

**O**VER THE COURSE OF MANY YEARS, Garza plans to use the devices to measure head impacts and correlate them to events on the field, such as a particular tackle. He and his colleagues also plan to collect head-impact data from the Stanford women's field hockey and lacrosse teams, which will be outfitted with the devices.

Garza, an assistant professor of orthopaedic surgery and medical director of the San Francisco 49ers, hopes the large quantity of data will help researchers develop a more accurate profile of the kinds of collisions that cause brain trauma, as well as more precise diagnostic criteria. "We need to get a better understanding of the epidemiology of these injuries," he says. "This study will build toward establishing clinically relevant head-impact correlations and thresholds to allow for a better understanding of the biomechanics of brain injuries. It also will serve as a helpful tool to aid in diagnosis and subsequent management of concussions."

**Nationwide, as many as 3.8 million sports- and recreation-related concussions occur each year, according to the Centers for Disease Control.** About 10 percent of all contact-sports athletes have concussions each year, according to the Sports Concussion Institute of Los Angeles.

A study of 1,913 NFL games played between 1996 and 2001 found that the rate of concussion was 0.41 per game, or slightly less than one concussion every other game. The rate is likely higher at the high school and college levels, where players often are still developing physically and don't have the strength and expertise of NFL players, Garza says.

In addition, he says, the injuries probably go underreported, given the difficulty of diagnosing them and the fact that some athletes may ignore their symptoms, knowing they will be sidelined if they speak up.

"One of the biggest problems is the uncertainty surrounding concussions," he says. "If you tear your ACL, I can say, 'Here's the injury on the MRI, and here's how we repair it.' So there's a confidence around treating those kinds of injuries. But diagnosing concussions is inherently subjective. Even traditional brain imaging will not pick anything up."

**Concussions occur when the brain is violently shaken. The shaking twists and tears connections between cells in the cerebral cortex, causing billions of them to depolarize and fire their neurotransmitters at once.** This in turn throws the brain's chemical balance out of whack, hindering the neurons' ability to start firing again. Many of these nerve cells then begin to shut down, which is why Hutchinson, the former Cardinal quarterback, said he felt drunk after his concussion.

Yet the fact that Hutchinson says he recovered fairly quickly and reported feeling no post-concussion symptoms in the hours and days following the injury is fairly good evidence that he suffered a mild concussion — what the American Academy of Neurology probably would have classified as grade 1, which often includes some transient confusion, grogginess, dizziness, balance difficulties and possibly other symptoms that resolve in less than 15 minutes. More serious concussions, like a grade 2, may cause post-traumatic amnesia and, in the case of a grade 3, loss of consciousness. Post-concussion symptoms are often experienced in the days and even weeks following the initial injury and may include headaches, fatigue, ringing in the ears, sleep problems, sensitivity to light and noise, poor concentration, and depression or anxiety. Such symptoms are the result of a severely discombobulated brain, one that has not yet regained its chemical equilibrium.

High-impact blows to the head and neck are the most common cause of the injury, says Stanford neurologist Jaime López, MD, who is assisting Garza with the study. "In a simple model — a linear model — your head is moving fast and then rapidly decelerates during impact," says López, "at which point some of this energy is absorbed by your skin and your skull and your cerebrospinal fluid, but the rest is absorbed by the brain, which is, of course, a quite delicate structure."

Rotational force is often involved in concussions and, according to some studies, may be an even bigger culprit than linear force, López says. An obvious example of rotational force would be when a player's head is struck from the side and whips around. To some degree, rotational forces are always at work in football collisions, which rarely occur along a simple linear plane. "Rotational forces tend to affect larger areas of the brain," López explains. "But the bottom line is there are complex mechanisms occurring, and we don't understand them completely."

Evidence suggests that people who already have sustained

# 'In theory, players

## CAN HAVE POST-CONCUSSIVE

SYMPTOMS THAT DON'T ALLOW THEM TO RETURN FOR  
A LONG PERIOD OF TIME ...'

a concussion are more vulnerable to subsequent concussions, but neurologists aren't sure why. There is also some evidence to suggest that genes may help determine a person's susceptibility to concussions.

For athletes, the practical question is how long they have to stay on the sidelines after a concussion. At Stanford, that answer depends on when they can meet a set of rigorous, exercise-based criteria, López says. After the concussion, athletes must pass a series of physical tests, beginning with low-exertion activities that become more strenuous over a number of days or weeks, depending on the players' tolerance levels. The exact amount of time a player is out depends on whether he or she can complete these exercises without triggering symptoms related to the concussion. "In theory, players can have post-concussive symptoms that don't allow them to return for a long period of time — maybe the rest of the season, maybe the rest of their lives," López says. But generally, players can return in a few days or weeks.

**Figuring out when a concussion has occurred is not straightforward. The more force behind a head impact does not necessarily translate into a greater chance of concussion, studies have shown.** In the January 2011 issue of *Exercise and Sports Sciences Reviews*, researchers at the University of North Carolina report that, according to their study, there was "no relationship between impact magnitude or location, and clinical outcomes of symptoms, balance, or neuropsychological performance." Football players sustained concussions over a wide range of magnitudes — from 60.51g to 168.71g of linear acceleration to the head, the researchers found, based on data collected from accelerometers in the helmets of Division I college football players. (One "g" is the force of Earth's gravity, so 60.51g is 60.51 times the force of gravity.) So what kinds of impacts *are* most likely to cause a concussion?

This is exactly the question Garza hopes to help answer with his study. And with Stanford's football, lacrosse and field hockey teams, he has a large and conveniently located subject pool. "It's a great opportunity for our student athletes, many of whom conduct scientific research in their academic studies, to contribute to the leading-edge research being done in sports medicine here," says Earl Koberlein, senior associate athletic director at Stanford. "It's a good marriage of the university's strong academics and strong athletics."

Last season, Scott Anderson, Stanford's head athletic trainer, and Jesse Free, an athletic training fellow, operated a computer on the sidelines that picked up data transmitted from the devices during football games and practices. Using video, the researchers were able to correlate this impact data to specific moments of a play.

Although there have been previous head-impact studies in football, they have relied on sensors embedded in helmets. Garza says it is possible the mouth guard data will prove more accurate, given that helmets sometimes shift on players' heads in a collision, which could throw off measurements. In any case, data from the current study will help illuminate earlier findings, he says.

It's still too early to draw conclusions from the data, the researchers say, and it's unclear whether any of the findings would serve helmet makers or lead to rule changes in football. Garza says he does not intend his study to diminish football or endanger its future. Rather, he hopes the data will enable physicians to better identify and care for players who have sustained a concussion or perhaps are at risk of long-term cognitive impairment because of cumulative injuries.

"Emotions are charged up around this, but to be honest I don't think we should jump to too many conclusions until we have larger studies," he says. "Concussions can happen in soccer, lacrosse and many other sports. My feeling is that as long as you follow best practices in managing concussions, we can still let people compete."

Hutchinson, who went on to play both professional football and baseball after graduating from Stanford with degrees in economics and political science, says he has seen teammates who took a lot of violent hits get right back up, seemingly unaffected, while others suffered concussions over and over again from less fearsome hits. "It makes me think there must be a genetic component," Hutchinson says.

He says he doesn't think the fear of concussions should deter people from sports they enjoy. "You don't want to live life like that," he says. "And I've known people who never played football get concussions. I know a guy who has had four concussions, and he got them water-skiing and falling off a ledge — things like that."

But how would he feel about one of his kids playing football? "I guess that would give me pause," he says. **SM**

Contact John Sanford at [jsanford@stanfordmed.org](mailto:jsanford@stanfordmed.org)

# TRANSITION POINT

## THE UNMET MEDICAL NEEDS OF TRANSGENDER PEOPLE

By TRACIE WHITE

PHOTOGRAPHY BY BRIAN SMALE

On a September morning about 10 years ago, Lyman Miller, PhD, showed up for an appointment with his family doctor in Half Moon Bay intending to ask for a prescription for female hormones. He was 57 years old, married for a second time, with two grown children. He stood over 6 feet tall, and sometimes wore a rough beard. And he wanted to become a woman.

His doctor, Lorraine Page, MD, thought she knew Miller fairly well. She knew he was a father and a husband. But she had no idea that since childhood he had felt he was truly female. "I'd never discussed this with any doctor," Miller says. "It took some psyching up. It was embarrassing. I was nervous." The doctor, understandably, didn't have a clue.

"He was a very masculine, confident kind of person," says Page, who knew Miller worked as an expert in Chinese foreign policy and domestic affairs at the Hoover Institution, a think tank on the Stanford campus. "But this visit, he was kind of awkward. There was some hesitation." So when

Miller mumbled something about wanting to get a prescription for hormones, the doctor assumed he meant testosterone for erectile dysfunction. Other male patients with similar requests had shown the same kind of embarrassment.

"But why?" she recalls asking. "I can get you a prescription for Viagra for that."

At right: Alice Miller, PhD,  
lived as a man for most of her life.  
Her primary care physician  
agreed to help her become a woman,  
but first had to learn how.





It took some time, and conversation, but eventually the two came to an understanding. Miller got a prescription for estrogen. And Page headed off to do research. Like most doctors, she knew very little about how to meet the medical needs of a transgender patient, particularly one headed down the road toward transitioning. But she was open to learning. Miller gave her some journal articles about recommended hormone dosages in such cases, and she turned to the Internet.

Page is far from alone in her unfamiliarity with transgender people and their treatment. The word “transgender” itself is often misunderstood. Transgender is an umbrella term that encompasses a range of non-conforming gender behavior, including crossdressers (who derive sexual stimulation from dressing in clothes of the opposite gender), drag queens and drag kings, and transsexuals (who feel their body does not match their innate sense of gender identity). Transsexuals may medically “transition” to the gender that’s right for them; others chose not to and so do not require the cooperation of the medical community.

Transitioning is the process of changing gender, which can take anywhere from a few months to years. Its endpoint can entail simply living openly in the new gender, or undergoing hormone therapy and sex-change surgery, or any variation of these steps.

The problem is that in the United States, most physicians don’t exactly know what treatment for the transgender patient entails. For an untrained professional, it’s a challenge to provide care to a patient with a penis who wants a vagina, or to a patient who has been tortured emotionally by being told she’s a boy when she knows she’s a girl.

General practitioners — the majority of doctors who treat patients in the United States — are equally unprepared to care for those transgender patients after they have begun to take hormones and undergone genital-reconstruction surgery. The lack of medical education on the topic, a near-total absence of research on transgender health issues and the resulting paucity of evidence-based treatment guidelines leave many at a loss.

About 700,000 transgender adults live in the United States, about 0.3 percent of the adult population, estimates Gary Gates, PhD, a demographer at UCLA’s Williams Institute, a gender-identity law and public-policy research group. As no national data on this population exist, Gates relied on two studies by state agencies, one conducted by California and the other by Massachusetts.

As for the need for medical care specific to transgender patients, here too only ballpark figures are available. Internationally known transgender-rights advocate Jamison Green, PhD, estimates that for most of the past 30 years, the number of patients undergoing sex-reassignment surgery remained

constant, around 1,000 a year. Recently, though, that figure appears to be creeping up, says Green, based on his informal observations of the health-care conferences and conversations with transgender people and practitioners. The growth of community-based transgender health forums is further evidence of interest. These forums have emerged in roughly two dozen cities throughout the country over the past five years. In 2011, the largest, in Philadelphia, drew thousands.

More transsexuals are also requiring ordinary medical

care that takes into account their uncommon status. Should a male-to-female transsexual be screened for breast cancer? What about a female-to-male? What are the special health risks for transsexuals as a population? These are just a few of the questions.

After decades of silence on the issue, recent landmark publications have helped bring attention to these growing needs:

In September 2011, medical students at Stanford published a study in the *Journal of the American Medical Association* on the lack of medical school education on health care for lesbian, gay, bisexual and transgender people. The study, which involved sending surveys to medical school deans across the United States and Canada, found that on average students received less than five hours of training. In addition, the deans made note of the specific lack of education on transgender care.

Earlier that year, on March 31, 2011, the Institute of Medicine had issued “The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding,” calling for more data and research to provide evidence-based care for transgender patients.

And on that same day, the *New England Journal of Medicine* published one of its first articles on the topic in its clinical practice series, titled “Care of Transsexual Persons” (by endocrinologist Louis Gooren, MD, PhD, of the VU University Medical Center in Amsterdam). The article points to the increasing



**Lyman Miller**  
worked hard at being male.  
As a young man,  
he played high school  
basketball and attended  
all-male Princeton  
University.  
Below: Miller during  
a trip to Yosemite  
with Avis Boutell  
after marrying in 1983.



numbers of transgender people seeking medical care in North America and discusses the need for studies on such topics as the safety of long-term, cross-sex hormone treatment.

**WHEN MILLER WAS 13, he came home from school each day, packed a knapsack and headed off to the limestone cliffs behind his home in rural western New York. Alone in the woods, he'd open the bag,** pull out a peanut butter sandwich, the hammer and chisel he used to hunt for fossils and, hidden down deep, an old dress of his mother's taken from the storeroom in his family's basement.

Miller liked to pull on the dress, then go exploring, digging for fossils and watching for birds. For these few hours, at least, he was free to be the girl he knew he was — a girl he named Alice. Then he would go back home dressed once again in pants, trying hard to be the boy the rest of the world expected him to be. When he turned 14, he put away the dresses hoping that if he tried hard enough to repress his feelings, they would vanish.

He spent much of his life trying to prove his manliness, especially to himself. He played high school basketball, attended an all-male Princeton University, entered the macho world of the CIA as an analyst. He married, had children and never told anyone that as a boy he so wanted to wear a dress like Queen Elizabeth's golden coronation gown that he secretly made himself a crown. Throughout his life, the shame of his secret self haunted him. He had no idea there was a name for how he felt or that there were others who felt the same. For most of his life he never conceived of the possibility of changing from male to female. Never did it cross his mind to discuss such feelings with a doctor. There was simply no point. Nothing could be done.

It wasn't until he caught a glimpse of a TV talk show when he was 52 that Miller even heard the word transsexual. And slowly, things began to change.

**TRANSGENDER PEOPLE are among the most marginalized individuals in the United States. Invisibility is often seen as a necessity for survival. Fears of eviction and job loss are rampant and well-founded,** says Walter Bockting, PhD, professor and coordinator of transgender health services at the University of Minnesota Medical School, who has cared for transgender patients for more than 20 years. On average one person is murdered every month in the United States because of transgender identity, according to the Transgender Legal Defense and Education Fund.

A survey of 6,500 transgender people by the National Center for Transgender Equality published in 2011 found pervasive discrimination in health-care settings. Among the results:

- 19 percent reported being refused care because of their

gender status.

- 28 percent said they were subjected to verbal harassment in medical settings.
- 2 percent reported being physically attacked in a doctor's office.

The survey also found widespread ignorance about the special health needs of transgender people, which can be substantial, even beyond the matter of transitioning. Participants reported rates of HIV infection at four times the national average, with the rates for male-to-female transsexuals the highest: 3.76 percent compared with the general population rate of 0.6 percent. The reasons for this high level are unknown but one likely factor is commercial sex work. Extreme marginalization within society and a resulting lack of self-esteem has led these women worldwide to prostitution for financial support, says Green.

Psychiatric care is perhaps the most desperately needed health service, with 41 percent of respondents reporting they had attempted suicide at least once.

These frightening statistics help explain why someone like Miller might spend years of his life in secret misery hiding his feelings. He was afraid of being called a freak, losing jobs, losing loved ones.

**AT THE AGE OF 52, Miller was teaching at the Johns Hopkins School of Advanced International Studies in Washington, D.C., when one day at home he noticed a *Phil Donabue* show featuring three women who had once been men referred to as transsexuals.**

The show shook him. He was amazed that he wasn't the only person who felt like he did.

Quietly, he once again began dressing in women's clothes. It was 1996. He had left the CIA to become a full-time academic. He was divorced with two children, had a well-established career as an expert in Chinese foreign policy, and was married to his second wife, Avis Boutell, whom he loved very much and who knew nothing about the feelings he had been suppressing his entire life.

Two years later, Miller finally spoke the truth. The neighbors glimpsed him in his backyard dressed as a woman, and he told his wife.

"I had tried to live a conventional life," Miller says.

**PHYSICIAN  
RESOURCES FOR  
TREATING  
TRANSEXUAL  
PEOPLE**

- Primary care protocol from UCSF:  
<http://stan.md/HuGz8x>
- Standards of care from WPATH:  
<http://stan.md/HuGUbo>
- The Endocrine Society's guidelines:  
<http://stan.md/Hrlpuh>





"But there was always this underlying, constant tension. Things just weren't right. I was aware from the time I was a little kid that I was a girl. I liked wearing girl clothes and playing with girls. I was embarrassed by my genitalia. My body was just wrong."

Most transgender people who transition from one gender to another while married lose their spouse. Boutell says she was confused and shocked, but she loved Lyman and eventually chose to stay with him.

"I knew nothing about transsexuals or anything," Boutell says. "So we started learning. ... After we decided that Alice should be Alice, it took me a long time to wrap my head around the fact that there is a person outside of gender. ... Alice is a pretty special person. I didn't want to lose her. I don't think I could ever love anyone as much as Alice."

The role of sex in this equation is often confusing for both partners and there are no clear-cut answers.

For Boutell and Miller, both nearing 60, sex became far less important than Miller's happiness. Miller was still attracted to women, but Boutell never was. "At first, I tried to be attracted to females," Boutell says. "But I'm just not." Sex became a non-issue. They just didn't have it.

Miller started the transition incrementally. After two years passed, he was dressing as a woman at home all the

**AVIS SAID,  
'YOU'RE GOING  
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TRANSITIONING?'**  
SHE TOLD ME TO  
GO SEE A  
THERAPIST.

time, but never in public. Boutell could see how much happier he was becoming. She taught him how to wear makeup, gave him manicures. It wasn't until the couple moved to California and Miller started new jobs there that he finally began to explore the possibility of transitioning full time into life as a woman.

"Avis said, 'You're going to be 60. Don't you want to be on the road to transitioning?' She told me to go see a therapist." Miller tracked down one of the few gender-identity specialists on the West Coast, Palo Alto-based Judy Van Maasdam, a social worker who has worked with transgender patients for 30 years, helping them understand the treatments and surgeries, prepare emotionally and find the health-care professionals they need.

For transsexuals seeking sex-reassignment surgery in the United States, preparation usually means following the international guidelines known as the "Standards of Care" set forth by the World Professional Association for

Transgender Health, or WPATH.

The standards require patients to give prospective surgeons letters from two therapists confirming a diagnosis of gender identity disorder, as described in the *Diagnostic and Statistical Manual of Mental Disorders*. And prior to genital surgery, they must live full time as the other sex for at least a year, taking the requisite hormone prescription regularly. While these are non-binding guidelines, most American surgeons refuse to operate unless the patient meets them.

In Miller's case, the transitioning process meant overcoming the embarrassment and fear of appearing to the world as female. [And from this point on, the story will refer to her as such.] It meant for the rest of her life she would take a daily dose of female hormones to help develop a more womanly figure with breasts and wider hips. It meant 250 hours of electrolysis to remove facial hair — three years of twice-weekly sessions that felt like rubber bands snapping repeatedly against her face — and then enduring the same torture to remove pubic hair in preparation for sex-change surgery. The amount of research, resources, time and money she expended to become a full-fledged woman was astounding. She talked to transgender men and women who had blazed the trail before her, searched websites, joined support groups, found self-help books, tracked down a trained surgeon. The final step, vaginoplasty surgery, she paid for herself at a cost of some \$20,000. Insurance coverage wasn't an option.

**TRANSGENDER PEOPLE** have been documented throughout history, but the possibility of physically changing the body to match a different gender didn't exist until the 1930s, when the first sex-change operations were conducted in Europe. The goal was to cure transgender patients of their emotional anguish through surgery and hormone treatments.

The treatment remained on the outskirts of the U.S. medical establishment until the 1960s, when greater funding for medical research and openness about sexuality set the stage for gender dysphoria clinics. The first was at Johns Hopkins University in 1966, followed by programs at the University of Minnesota, UCLA, Northwestern University and Stanford. In 1966, Harry Benjamin, MD — a physician who experimented with hormone treatments — wrote his groundbreaking book, *The Transsexual Phenomenon*, which provided the initial guidance to health professionals working with this population.

But by the mid-to-late 1980s, the field had declined. Most gender dysphoria programs were shuttered by universities because of a controversial study casting doubt on the programs' value, shrinking funding and changing social mores. Clinics either moved off campus or disappeared altogether. Many

scaled down their services, no longer offering surgery or prescribing hormone therapy. At Stanford, the gender dysphoria program became an independent clinic and moved across the street from the university, where it's still in existence. Only two U.S. universities — the University of Minnesota and the University of Michigan — still operate gender clinics, and those refer out genital surgeries for transsexuals. In fact, few if any hospitals at U.S. academic medical centers conduct the surgeries. So where do patients go? Many go to Thailand or Belgium where the costs are lower and the frequency of surgery much higher — two or three a day. If the patient stays in the United States, the surgery will be at one of the hospitals where the few U.S. surgeons trained in genital surgery practice. The male-to-female surgery — called vaginoplasty or vaginal construction — will cost about \$20,000 to \$30,000. The female-to-male surgery is much more expensive — with variations ranging from \$35,000 to \$100,000, with results often less than perfect. The way most surgeons describe it, it's much easier to take away than add on.

Today, as a field of medicine, transgender care is virtually nonexistent. Training for specialists in sex-reassignment surgery is rare, says Gordon Lee, MD, assistant professor of plastic and reconstructive surgery at Stanford. "It's not taught in surgical residencies. Medical schools and students know nothing about it. It is done by a few surgeons at a few locations. Not a lot will publicize that they do this surgery. There's a stigma about doing it."

And in the United States, scarcely any research has been conducted over the past 30 years.

**THERE ARE SIGNS** of improvement, in part because of pressure from the transgender community and their advocates, and in part because of recognition by the medical establishment of the need. With more exposure in the media, on the Internet and in workplaces, the growing acceptance of transgender individuals in general has begun to trickle into the medical world.

"Times have turned," says Bockting of the University of Minnesota's transgender health services. "The medical needs of transgender patients are being recognized more so than ever before." He points to a new residency elective at his medical school, a three-week rotation available to family medicine, psychiatry and ob/gyn residents shadowing physicians who do physical examinations and hormone therapy.

A new push for better education on the topic in medical school reflects the change within the medical field. Much of transgender care has moved from specialty clinics into primary care settings where family doctors are prescribing hormones and providing that first line of treatment.

These doctors are looking for help to treat their patients.



"It's pretty straightforward," Bockting says. "With some training and guidance a family doctor can provide this care."

The March 2011 *New England Journal of Medicine* article points to WPATH and the Endocrine Society as good sources for treatment guidelines.

**MILLER HAS COME a long way from that initial embarrassing doctor's visit 10 years ago. Today, Lyman Miller lives full time as Alice Miller:** a 6-foot-1-inch, 67-year-old woman with manly hands and a way of tilting her head to the side when she listens that is utterly female.

Miller has kept a chronology of the steps that led to her transition. It stretches from August 2002, when she first began regular sessions with Van Maasdam, to vaginoplasty surgery at Sequoia Hospital in Redwood City, Calif., on Aug. 31, 2007. It recounts the many steps in between that led to her transition — from applying that first estrogen patch, to filing a petition with the San Mateo County courts to legally change

her name, to packing up all her "guy clothes" and donating them to a thrift store.

Miller's greatest fears, which revolved around telling her children, her wife and her bosses, proved unfounded. When she made her transition, she worked not only at the Hoover Institution but at Stanford's Department of Political Science and at the U.S. Naval Postgraduate School in Monterey, Calif. All three said they had former employees who had made similar requests. All proved supportive. Her two grown children were surprised, but encouraging. Only Boutell's son from a previous marriage refused to allow the couple to see his two children, causing Boutell untold grief.

"I should have done it a million years ago," says Miller, her voice deep but soft, her shoes flat but feminine, all trace of the once-heavy beard, gone. "But I was terrified I would lose my whole life."

Today, Miller says she has no regrets about transitioning. "Next to marrying Avis, it's the best thing I ever did," she says.

## FEATURE

### Brain power

CONTINUED FROM PAGE 11

The fMRI results of the Stroop test are of more than academic interest: They have implications for treatment. In addition to being used to develop the computerized cognitive behavioral exercises, the Stroop task, for instance, may be able to serve as a marker to guide more effective use of antidepressants. Although not everyone with depression benefits from these drugs, certain drugs appear to be effective in some cases. The hope is that a set of clinical and biological markers can be developed that will make it possible to identify which drug will benefit which patients. Etkin's lab is involved in studies that include hundreds of people with depression. It's possible that a patient's Stroop results can help indicate which treatment to pursue.

Along the same lines, Etkin is using the Stroop task and fMRI scans to evaluate how people with PTSD symptoms benefit from exposure therapy, in which they are exposed to the source of their fear. (It works in about half of all cases.) This is a step toward understanding how the treatment works biologically and whom it could help. As part of this research, Etkin's lab is exploring a new treatment, transcranial magnetic stimulation, a noninvasive technique that induces electric currents in specific brain regions and thereby alters their activity. The study uses imaging to see whether TMS can change PTSD patients' brain function in the same way as effective exposure therapy.

**Five or so years ago, advances in fMRI research, genetics and molecular biology had been expected to provide a new basis for diagnoses** in the forthcoming edition of the *Diagnostic and Statistical Manual of Mental Disorders-5* — often referred to as psychiatry's bible. The manual's editors now readily admit that they were overly optimistic and that such a shift is not yet possible. Nonetheless, the new *DSM* is being designed so biological criteria can be added online in the future. What's more, the NIMH last year launched an effort, known as the Research Domain Criteria Project, to develop an alternative to *DSM* that involves rethinking the entire classification system of psychiatric disease, based on neurobiology.

To grasp why such efforts could be turning a corner despite past disappointments requires understanding three big reasons psychiatric research has lagged behind other medical disciplines — and why recent developments suggest that these obstacles can be overcome.

1. Where do you find a schizophrenic mouse? Mouse models, the basis of much medical research, are hard to apply to psychiatric disorders.

In recent years, genetic sequencing has enabled researchers to engineer mice that have mutations similar to those discovered in certain psychiatric conditions. While pinpointing genetic causes of mental illness has been more complex than anticipated, advances in sequencing technology and genetic databases have lately yielded some signifi-

cant findings, including the identification of seven "copy number variations" — small chunks of DNA deleted or duplicated at a given spot in the genome — that increase by 10 times the likelihood of developing schizophrenia. "Never in history — the 100 years that we've been researching this black box — has anything been discovered that would raise your risk of schizophrenia by 10 times," says Douglas Levinson, MD, a Stanford psychiatry professor who has contributed to the research. He is quick to make a caveat: These mutations account for no more than 1-2 percent of those with schizophrenia. Still, the discovery paves the way for creating mice with these genetic anomalies; that would, in turn, allow scientists to study how these mutations affect neuron function and develop insights about brain activity characteristic of schizophrenia.

2. How do you get a piece of someone's brain? Biopsy samples from study participants, a staple for research in other medical disciplines, are not available to psychiatric researchers.

Included in NIMH director Insel's top 10 research advances of 2011 is a technique called "disease in a dish." Essentially, it's now possible to take a skin cell from someone with a psychiatric disorder and transform it into a neuron. "For the very first time, you can make these tissues that you could not access normally," says Ricardo Dolmetsch, PhD, associate professor of neurobiology, describing how he has used skin cells from patients with Timothy syndrome, a



For now, with a lack of evidence-based care and insufficient medical school training, many primary care doctors are still on their own searching the Internet for information, pounding the pavement for experts and asking their transgender patients about what kind of care they need.

It still takes some work and research to track down accurate and helpful information, says Green. But it can be done. He points to new guidelines developed by the University of California-San Francisco for such routine concerns as patient intake forms that the Centers for Disease Control is adopting. In addition to WPATH and the Endocrine Society, the Vancouver Coastal Health website is fairly up to date and helpful, he says.

"It's not rocket science to provide primary care, including hormones, to transgender or transsexual patients," says Green, who is himself transgender. "It just takes a little awareness, conscientiousness and a genuine respect for us as human beings." Physicians should be cognizant that sex-change surgery patients often still carry reproductive organs from be-

fore, and these may need continuing medical attention. That's something that can be easily missed, says Nelson Teng, MD, associate professor of obstetrics and gynecology at Stanford, who has treated several female-to-male transsexuals for endometrial cancer — cancer of the lining of the uterus. "Many male transgender patients still have a uterus and still should see gynecologists."

For Miller, 2011 was the first year she underwent a full physical as a woman, which included a breast exam and a mammogram. After about five years of female hormones, her prostate had greatly diminished in size. Page, her family doctor, wasn't sure what to do, so she tracked down a San Francisco surgeon familiar with transgender care who advised her that it was OK to stop the exams. The prostate was too small to worry about.

"You do feel like you are experimenting sometimes," Page says. **SM**

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rare genetic disorder in which children show autism-like symptoms, "to generate little pieces of brain." By studying these samples, he has identified abnormalities in synapse formation and levels of neurotransmitters, which offer new opportunities for developing treatments.

**3. Can you test-drive a neurocircuit?** The brain's complexity has made it hard to pinpoint cellular mechanisms that cause psychiatric disease and to test therapies.

While fMRI studies such as Etkin's are a big step forward in understanding brain function, the technology does not definitively determine cause and effect. And fMRIs measure brain function by voxel, a segment of brain about the size of a grain of rice, which is comprised of millions and millions of neurons. There is, however, a new technology, optogenetics, that can determine — on a cellular level — what causes changes in behavior symptomatic of psychiatric disorders. (It's used only used in lab animals, as manipulating human brain cells in this fashion is seen as way too risky.) Karl Deisseroth, MD, PhD, a Stanford associate professor of psychiatry and of bioengineering, has pioneered this technology, which involves engineering a highly select group of neurons so that they can be switched on and off by pulses of light, usually delivered by fiber optic cable to the brain region of interest. Using this technique, he has discovered how to target particular neurons that cause behavior changes relevant to narcolepsy, cocaine addiction, autism and anxiety.

Interestingly, in his study on anxiety, Deisseroth chose to focus on neurons in a sub-region of the amygdala in mice that is in roughly the same spot in humans that Etkin has shown to play a role in anxiety disorders. "Amit showed that there was altered activity in some interesting areas of the amygdala, but we didn't know if it was causative or correlative," Deisseroth says. The optogenetics test clearly shows the former. By stimulating particular cells with light, Deisseroth and his colleagues caused mice to behave in a markedly less anxious manner. "We are driving the neurons that inhibit amygdala output."

And that may provide a new mechanism to target with a new class of drugs.

**"Your data are really nice," Etkin tells me a week after my fMRI,** as he calls up on his computer the scans that have been composed from my performance on his Stroop task.

The scans show how my brain response differs after seeing consecutive "incongruent" images (the mismatched expressions and emotions, i.e., smiling face with the word "fear") as compared with my seeing an incongruent image after a congruent one (i.e., smiling face with the word "happy").

In my brain scans, there are about eight blue splotches and a few dabs of red. The former shows the regions that are less active, while the latter shows those that are more active.

Etkin points to the brightest red fleck that is just above my forehead. "There you're activating your ventromedial pre-

frontal cortex," he tells me. He then points to the blue that starts up at the top of my head and swoops toward the back of my head and down to the center of my brain. "As you engage, you also dampen the dorsal medial prefrontal cortex and the lateral prefrontal cortex, and you dampen activity in the amygdala," he says.

Etkin calls up a diagram from one of his papers that is a composite of responses from participants who were considered healthy. It is shockingly similar to my own picture. "What we see with you is pretty close to the typical," he says, alternating the screen between the two images. "Look at the similarities — it is a beautiful overlap."

Etkin tells me that I made five incorrect identifications, which means that I was in the norm and that my response times were as well, with my getting increasingly fast when shown two consecutive incongruent images.

The interview with Etkin is in no way an assessment of my mental health, but it's definitely a new way for me to think about it.

Later I print the scans and hang them on my refrigerator door. Occasionally a visitor asks me about them. I say they show a neural network we all rely upon to deal with emotional conflict. I point to the activated red spot and the dampened blue blobs and explain that they show how people cope with anxiety.

This is what it's supposed to look like, I tell them, in a normal brain. **SM**

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## FEATURE

### Autism

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from a private therapist after school, Cartwright told the school she wanted to discontinue Katie's in-school speech therapy. "They were shocked," she recalls. "They said, 'Nobody's ever turned down speech.'" Eventually the school offered a compromise, rescheduling Katie's speech therapy at a less disruptive time of day. Katie started acting out much less.

#### THE HOMEWORK EXPERIMENT

Many parents worry, as Cartwright did, about the consequence of discontinuing treatments, even when that decision is clearly best for the child. "Just the mere fact that you adopt an intervention can make you reluctant to stop it," Berquist says, adding that if parents take nothing else away from her class, having that one small fact about

human cognition in their possession can have a big impact in the long run.

To help parents collect the best available information for making difficult treatment decisions, Berquist's students learn single-subject study design, developing testable hypotheses and collecting and analyzing data on their children's behavior. Cartwright decided to apply these lessons to a problem with Katie's homework sessions. The two worked together each evening, but Katie often complained instead of concentrating, saying "I can't do it" or "I need help" about tasks that she really could do on her own.

Berquist suggested a simple intervention: Cartwright could leave Katie alone to see if less attention from Mom would improve her focus. So Cartwright set up a series of trials. She sat Katie down with some easy worksheets, trained the video camera on her and said, "I'll be in the other room; I'm coming back in half an hour."

The first time, Cartwright recalls, Katie "threw a really extreme tantrum." On subsequent days, Katie spent 10 or 12 minutes complaining loudly, tossing down her pen and putting her head in her arms and groaning. But the duration of her unfocused behavior soon lessened, as a neat line graph displaying the data in Cartwright's binder shows. After four days Katie was settling down to work in less than three minutes each day. Cartwright was thrilled.

Then Berquist coached Cartwright to reverse the intervention — a key step in demonstrating a genuine cause and effect.

"I didn't want to," Cartwright says with a laugh. But she tried it, and Katie acted up once more.

Cartwright re-instituted the unwatched homework sessions, and Katie quickly regained her improved focus. "I was surprised how fast it was obvious," Cartwright says.

## FEATURE

### The neuroscience of need

CONTINUED FROM PAGE 27

but on the degree to which it meets expectations. The juice still tastes great, but it's no longer a surprise; it's predictable. However, the light's timing can't be predicted. It's always a surprise, and (as the animal now knows) it's always a prelude to something good.

The reward circuitry is always secreting dribs and drabs of dopamine. If an experimental animal gets a bigger-than-expected reward, the frequency and amount of dopamine secretion increases; if it's smaller than anticipated (or if the light goes on but the animal's frantic lever-pressing brings no juice at all), dopamine secretion drops below baseline levels. Moreover, this depression in firing rates of dopamine-secreting neurons occurs precisely when the anticipated reward should have come, but didn't. Thus, the brain seems to interpret the absence of the expected reward not merely as a lack of enjoyment but as a punishment. (How does a rat spell "disappointed"?)

Sam McClure, an assistant professor of psychology at Stanford who studied un-

der Montague, has been imaging human brains to visualize connections between the regions that constitute the reward circuit. "Variations in dopamine levels tell all kinds of structures in your brain when something you want is within reach, getting closer, slipping away or not working for you anymore," he says.

At least that's the way it's supposed to work. Cocaine, heroin and other abused substances usurp this system. And they do it in a really creepy, pernicious way: by short-circuiting it.

With normally rewarding things like food and sex, we usually have a pretty good idea of how good it will be. It's when the reward exceeds our expectations that the dopamine circuitry really lights up big time. Conversely, if our expectations aren't met, dopamine activity drops off.

But cocaine, heroin, alcohol and nicotine directly activate the circuit — they goose dopamine secretion — regardless of how high the expectation was. "Every time you take it, you activate that dopamine activity, so you're getting a readout that says, 'Wow, this was even better than I thought it would

be,'" McClure says. "It's always better than you expected. Every single time." The experience is remembered as always getting better — even if, paradoxically, it's actually not so great anymore. ("Tolerance mechanisms" within the brain can cause a drug's pleasant effect to diminish with repeated use.)

#### The needle and the damage done

IN SUSCEPTIBLE INDIVIDUALS, REPEATED DRUG USE CREATES the same kind of lasting changes in the connections among neurons that we get from learning to ride a bike.

One important way our brains snap an experience into long-term memory is by strengthening the synaptic contacts between neurons in the network that encodes this experience. This involves a number of biochemical changes in both the bulb protruding from a neuron's axon and the brush-like extension of a nearby neuron. Drug abuse can also cause neurons to sprout brand-new synapses — for example in the nucleus accumbens, the hotspot for positive emotions. It can weaken synapses, too. Nora Volkow, MD, of the National Institute on Drug Abuse has shown that the plan-

## BECOMING MORE OBJECTIVE

Videotaping Katie has had other benefits, too. "Not only do I see Katie's behavior, I also see my tone of voice, my interactions with her," Cartwright says. The scientists' approach of evaluating specific aspects of Katie's behavior has helped Cartwright make decisions about her child more objectively. "Instead of getting emotional — 'It's my kid, she's not progressing!' — this is more scientific," she says.

Berquist agrees, pointing out that the methods she teaches could fill two gaps in autism research.

First, conducting research on autism therapies is difficult. Gathering groups of children for randomized controlled trials takes years of work and millions of dollars. Berquist hopes eventually to digitize the data her students collect and, with their consent, publish it in a searchable form that other parents can access — not

a replacement for randomized controlled trials, but still a way to broaden the scientific knowledge base for understudied autism therapies.

Second, even when treatments work for large groups of children with autism, scientific studies can't predict how effective a therapy will be for a specific child. That means the studies lack the information parents want most. "Many parents will say, 'I don't care if there's research,'" Berquist says. "For them, it comes back to their kid."

And that's a gap that this method is perhaps uniquely able to fill:

"Are you spending money and energy on something that will work for your particular child?" Berquist asks. "This is the best way to find out." **SM**

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oriented prefrontal cortex functions poorly in cocaine addicts.

The long-term strengthening of drug-associated memory circuits, combined with that "even better than expected" illusion addictive drugs foist on users, goes a long way toward explaining what is probably the biggest problem addicts and those who treat them face: a pronounced tendency to slide back into the habit. It's why former White House drug-policy advisor Humphreys believes long-term treatment is vital.

If you are an addict, not just the drug but also all the associated physical, geographical and social cues exert a powerful effect, even decades after the last time you were anywhere near the drug: You walk past the bar you used to get drunk in and see your buddies in there, or you smell cigarette smoke — or, if you used to inject cocaine or heroin, all it may take is seeing a spoon — and you experience a craving and risk a relapse. Stress — you lose your job, suffer a divorce, undergo a financial crisis — can mimic drugs' influence on the reward circuitry, and is therefore another major cause of relapse.

### Who's susceptible? (Who knows?)

ONLY A FRACTION OF PEOPLE WHO EXPERIMENT WITH DRUG USE get addicted. But virtually all of us have an intact, functional reward system. So why wouldn't we all be subject to the tyranny of drug-induced illusions of "better-than-expected-ness?"

The short answer is that nobody knows enough to be able to single out a potential addict with any certainty. "There's no such thing as an 'addictive personality,'" says Humphreys. "Those 25 million addicts in the United States have wildly different personalities." There are, however, obvious risk factors: genetics, poor social support networks, a sense of having nothing to lose and stress.

One big risk factor, says Humphreys, is the age at which you start using. "We're the most vulnerable to addiction in our early teenage years, when our brains are most plastic. So it's not an accident that almost every single adult smoker started smoking when they were teenagers. If you start smoking when you're 30, you are almost certainly not going to get addicted. But the younger you start, the more likely

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you are to keep smoking.

"There are two groups of people who really understand that: prevention professionals, and the tobacco companies. You want to make addictive substances as inaccessible as possible in the environment, particularly for young people."

The biggest risk factor of all, of course, is the initial use of an addictive substance, says Malenka. "It's impossible to get addicted if you never take the drug." **SM**

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# TRUE REFLECTION

## THE POWER OF AN ARTIFICIAL STEM CELL

Barry Behr, PhD, preps for surgery with deep, calming breaths. Each incision that follows has to be precise enough to slice an object a tenth the size of the period at the end of this sentence. There are no do-overs. Using a laser, he tediously grazes an embryo, causing the shell to crack and spill its goopy contents into the liquid milieu of the petri dish. • “This is called ‘assisted hatching,’” Behr says as he glances up from the laser-equipped microscope in the center of his spotless in vitro fertilization lab.

He normally performs this micro-operation only on embryos he’s preparing to implant into a hopeful mother-to-be. But last year, he used it for an experiment comparing embryonic stem cells with artificial ones — called induced pluripotent stem cells, or iPS cells. He and his colleagues wanted to know if iPS cells could replace embryonic stem cells — a gold standard for studying disease.

Behr collected stem cells from an embryo carrying a mutation for Marfan syndrome — a condition that affects connective tissue, causing extra-long limbs, tall height and cardiovascular problems. His collaborators

used ordinary skin cells from an adult Marfan patient to engineer iPS cells.

“We had both types of stem cells side by side, both containing the defective gene responsible for Marfan. This was a perfect opportunity to compare them,” says surgeon Michael Longaker, MD, senior author of the study, which was published Jan. 3 in *Proceedings of the National Academy of Sciences*.

They found the iPS cells perfectly mirrored Behr’s embryonic cells, establishing an easier, less controversial alternative for life-saving research. But collecting the embryonic stem cells wasn’t easy.

An IVF patient with Marfan syndrome donated the week-old embryo after Behr “spell checked” its genetic code and found that it harbored an error in the gene Fibrillin-1, the root of Marfan symptoms. In addition to an assisted hatch, Behr used the laser to cull the dense, stem-cell-containing



Barry Behr uses a laser to crack an embryo and release the inner cell mass — the source of embryonic stem cells. The cell mass, not yet emerged, is at the embryo's left side. Magnification: 500x.

inner mass — similar to the yolk of an egg — from the rest of the embryo. The maneuver carries only a 20 to 30 percent success rate. And Behr had only one embryo, one shot.

“This is where spatial memory comes in handy,” Behr says. He places an embryo-containing petri dish on the microscope’s platform for a demonstration viewed on its monitor. To keep the microscopic ball of cells from spinning in its liquid buffer, Behr uses two tiny, joystick-controlled glass straws that apply gentle suction from both sides. Once he sucks the embryo in place, he uses his mouse to aim the laser at the stem-cell-harboring mass that looks like a wad of gum stuck to the inside of a bubble.

With the straws steady, Behr shoots with consecutive clicks of a foot-pedal trigger, cutting through the embryo one laser blast at a time. If it spins or floats away, he has to remember the orientation of the wad. It’s a painstaking process, to say the least. Once the clump is completely severed, his collaborators plunk it into stem cell nutrient broth for months to ensure he sliced out only the stem cells. It took a year to authenticate the Marfan embryonic stem cell line.

“It certainly would be a lot easier to have an alternative cell line without this slicing and dicing,” Behr says. What’s so cool about the group’s study — cooler than a laser-firing microscope, he says — is that they proved they had one. — BETH MOLE

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## It hurts!

### TAKING THE TEMPERATURE OF PAIN

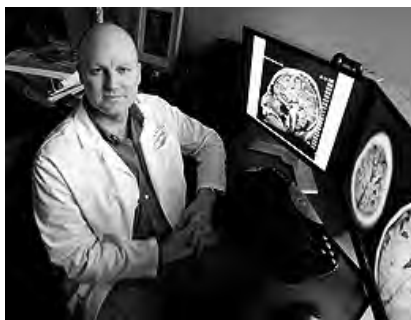
IT WAS A SIMPLE, PAINFUL EXPERIMENT. • HOW PAINFUL? THAT'S EXACTLY WHAT THE EXPERIMENT SET OUT TO DISCOVER. • "People have been looking for a pain detector for a very long time," says Sean Mackey, MD, PhD, who led the project to develop the first "painometer." "We rely on patients self-reporting for pain, and that remains the gold standard. But there are a large number of patients, particularly among the very young and the very old, who can't communicate their pain levels.

"We're hopeful we can eventually use this technology for better detection and better treatment of chronic pain," adds Mackey, chief of the Division of Pain Management and associate professor of anesthesia. He published the study Sept. 13, 2011, in *PLoS ONE*.

Mackey and his colleagues scanned the brains of eight subjects, using functional magnetic resonance imaging. To induce some pain, they applied a heated probe to the subjects' forearms. The team recorded brain patterns both with and without pain, and used the patterns to train a computer algorithm to create a model of what pain looks like.

The computer was then asked to consider the brain scans of eight new subjects and determine whether they had thermal pain.

"It did amazingly well," says co-author Neil Chatterjee, currently an MD/PhD student



**Sean Mackey**

at Northwestern University. The computer was successful 81 percent of the time.

The idea for this study arose at a 2009 Stanford Law School forum on how the neuroimaging of pain could be used and abused in the legal system. Mackey attended with two of his lab assistants — Chatterjee and Justin Brown, PhD, now an assistant professor at Simpson College.

"At the end of the symposium, there was discussion about the challenges of creating a painometer. I discussed hypothetically how we could do this in the future," Mackey says. Afterward, Chatterjee and Brown decided to give it a shot.

"It was very much on a whim," says Chatterjee. "We thought, maybe we can't make the perfect tool, but has anyone ever really tried doing this on a very, very basic level? It turned out to be surprisingly simple to do this." — TRACIE WHITE

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