Today's mind-altering drugs can already improve your memory, increase your alertness, and smooth your

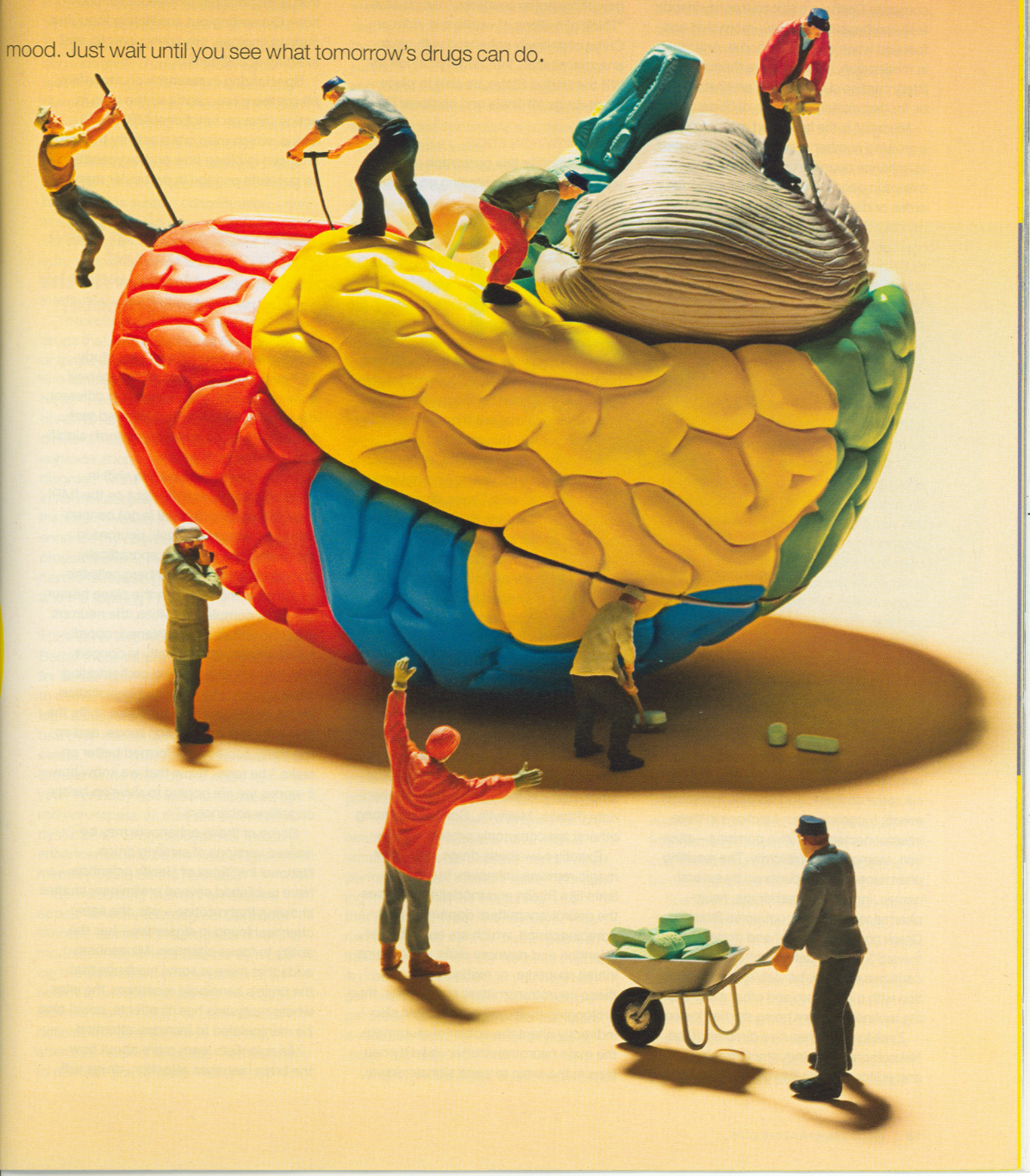
BUILDING A BETTER BRAIN

by Sherry Baker

At a party in a rambling, million-dollar Victorian mansion in Atlanta's hip Inman Park neighborhood, artists and lawyers, musicians and businesspeople mingle, talk, and imbibe that eternally popular feel-good drug, alcohol. The slightly pungent scent of marijuana drifts in from a room off the kitchen, where joints are passed among a dozen people, some of them old enough to have been smoking marijuana as a recreational drug since the 1960s. Despite the fears of their worried parents in the hippie heyday, most of these folks have ended up successful; they say that they are using pot to unwind, de-stress, and be more sociable.

Later I join some friends and head to a nearby tavern. Here we are, four middle-aged professionals (a physician, a neurology technician, a computer executive, and a writer) having beers and burgers, when the conversation turns to travel—and to a certain drug. Everyone but me is knowledgeable and enthusiastic about this attention enhancer, which has become de rigueur for their far-flung travels abroad. Used routinely on trips that would normally leave people jet-lagged, the drug helps over-

mood. Just wait until you see what tomorrow's drugs can do.



ride weariness from disrupted circadian rhythms and broken sleep. The small pill, containing the compound modafinil and marketed as Provigil by the pharmaceutical company Cephalon, also makes my friends feel—perhaps actually *be*—more alert and focused when they return home. And taken in moderation, it doesn't give them the jittery cardiac stimulation of amphetamines or, for that matter, too much caffeine.

Modafinil is the latest and most touted of a growing number of pharmaceuticals used to enhance cognition and mental performance in people without a diagnosis, disorder, or disease. The trend I observed on my party circuit has been documented in rigorous peer review: In a study published last year in *Pharmacotherapy,* researchers at the University of Maryland found that of 1,208 college students, 18 percent took ADHD medications like Ritalin and Adderall even though the drugs had not been prescribed. You might think the college students were taking stimulants mostly to party, but that is not what the researchers found. The students were taking the stimulants mainly to help with studying.

College students are not the only ones seeking that attention edge. According to an informal survey conducted by *Nature* last year, 20 percent of the more than 1,400 responding readers admitted to using cognition-enhancing prescription drugs for nonmedical reasons, mostly to "improve concentration." Of those, some 50 percent said they did it daily or weekly. These were not just twentysomethings, either; nearly half of the respondents were over 35.

Drugs like modafinil, moreover, are just the leading edge of a growing trend. The potential for mind-boosting drugs and technologies has increased stunningly over the past decade as neuroscientists have unlocked the secrets of neuronal circuits, neurotransmitters, and specific molecular events triggering brain functions in three interconnected cognitive domains—attention, memory, and creativity. The resulting pharmaceutical products go by several names, including smart drugs, neuropharmaceuticals, or nootropics (from the Greek *noos,* for "mind," and *tropein,* "going toward"). In applications where pharmaceuticals may not be viable, brain stimulation with magnetism and other mind-altering technologies are being studied instead.

Zack Lynch, executive director of the Neurotechnology Industry Organization and editor of *Brain Waves,* an industry blog, predicts these products will transform our future. "Neurotechnology holds the promise of not only changing people individually but accelerating economic growth for entire countries," Lynch says. "Think of millions of workers in India or China cognitively enhanced with neuropharmaceuticals that boost productivity. Will the United States be able to place these drugs off-limits and compete?"

THE ATTENTION EDGE

Pay attention to this paragraph and you are selectively concentrating on a task or idea while ignoring distractions like that dog barking down the street or your cell phone ringing. In a world of information overload and increasing multi-multitasking, you do not have to suffer from ADHD to have trouble focusing. You need no diagnosis to benefit from drugs that cut through the chaos and help you get things done.

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Attention-focusing drugs, of course, have been here for years: Amphetamines, nicknamed "go pills," were discovered in the late 19th century. By the 1940s these central nervous system stimulants were widely used to treat asthma and had become popular as "pep" and diet pills. They were embraced by members of the armed forces, especially pilots, who had to remain attentive to myriad tasks despite constant danger and fatigue. Rife with serious side effects, including hallucinations, anorexia, and heart problems, dextroamphetamine (trade name Dexedrine, better known as speed) is rarely used today by civilians. But the amphetamine mix Adderall and the amphetamine-related drug methylphenidate (Ritalin, Methylin, Concerta, among others) are commonly prescribed.

Exactly how these drugs work their magic remains unknown, but stimulants like Ritalin and modafinil influence the neurotransmitters dopamine and norepinephrine, which are essential for attention and memory skills. Both drugs inhibit reuptake, or reabsorption, of these neurotransmitters by neurons, thus prolonging their action. Modafinil also indirectly alters the action of glutamate, the main neurotransmitter used by neurons in the brain to send signals down the line. The center of action for all these drugs, says University of California at Davis psychiatrist Michael Minzenberg, is the prefrontal cortex, the part of the brain that is responsible for executive functions like sorting out conflicting thoughts, making choices, predicting events, and exerting social control.

Specializing in research on modafinil, Minzenberg has captured the drug in action through functional MRI (fMRI) scans, which map brain activity through changes in blood flow and oxygenation as subjects engage in particular mental processes. In one Minzenberg study, 21 healthy research subjects received either modafinil or a placebo on different days as they took a standardized test. Modafinil helped subjects perform significantly better on the task.

Researchers also saw the shift in prefrontal cortex activity right on the fMRI map. When an individual is not concentrating on a complex task, neurons in that part of the brain fire sporadically, constituting what Minzenberg calls the exploration mode. When the same person performs complex activities, the neurons shift into a state of heightened, coordinated activity, firing mostly in concert with the task at hand and orchestrating what Minzenberg terms the exploitation mode. "We found that modafinil shifts the brain into this exploitation mode, and so the study subjects performed better on tasks," he says. "Now that we know how it works, we are hoping to develop better cognitive enhancers."

Some of those enhancers may be revised versions of existing drugs. National Institutes of Health scientists have published several preliminary studies showing that nicotine—yes, the same chemical found in cigarettes—has the ability to focus attention. Minzenberg adds that there is some evidence that the brain's canniboid receptors, the sites where marijuana has its effects, could also be manipulated to increase attention.

As scientists learn more about how the brain manages attention, drugs will

become ever more powerful, nuanced, and precise. Neuroscientists Timothy Buschman and Earl Miller of the Massachusetts Institute of Technology, for instance, have found two types of attention in two separate regions of the brain. The prefrontal cortex is in charge of willful concentration; if you are studying for a test or writing a novel, the impetus and the orders come from there. But if there is a sudden, riveting event—the attack of a tiger or the scream of a child—it is the parietal cortex that is activated. The MIT scientists have learned that the two brain regions sustain concentration when the neurons emit pulses of electricity at specific rates—faster frequencies for the automatic processing of the parietal cortex, slower frequencies for the deliberate, intentional work of the prefrontal.

Theoretically, a spectrum of different drugs that modulate neural frequencies or target specific areas of the brain could fine-tune attention to suit the task at hand. "People may have different forms of ADHD. By tailoring drugs for these two different frequencies, we may be able to enhance attention for specific forms of the disorder," Miller says. As for moderate use in normal people, he has no problem with the idea: "I would love to have drugs that enhance my cognition." When the new products arrive, there may be different flavors for the surgeon, the fighter pilot, and the aspiring Ph.D.

MEMORY: THE NEW SEX

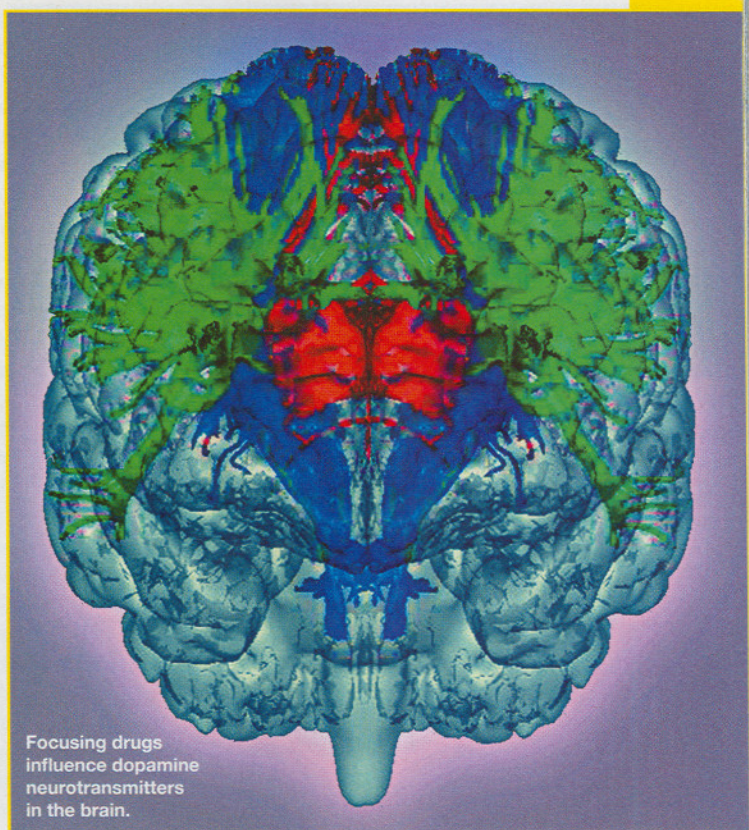
Better focus naturally feeds the desire for better memory. "Already, you go to dinner parties and the middle-aged high achievers talk more about how bad their memories are than about real estate," *New York Times* columnist David Brooks wrote in an op-ed piece last year. For baby boomers as stressed by memory lapses as they are by erectile dysfunction, Brooks suggests, memory enhancers could be the new Viagra, and memory could be the new sex.

Some existing memory enhancers appear to work, to a degree. Donepezil (Aricept) can slow the progress of mild to moderate Alzheimer's disease by blocking the breakdown of acetylcholine, a neurotransmitter that carries messages between nerve cells. For patients with deficits, the drug improves memory, attention, reason, language, and the ability to perform simple tasks—for a time.

In normal people, the results are mixed. A U.S. study of healthy young and older subjects who took donepezil for only 14 days found that performance on short-term memory tasks actually deteriorated slightly. But a German study looked at the performance of healthy young male subjects who took the drug for 30 days and found that it selectively improved immediate recall in a verbal memory test and improved immediate and delayed recall on visual tasks.

Better memory boosters now in clinical trials should be here in four to five years. Among the most promising are the ampakines, a class of compounds that keep glutamate receptors open longer, allowing more of that critical neurotransmitter to enter the cell. Cortex Pharmaceuticals in Irvine, California, the company spearheading much of the work, reports that the compounds can slow or even halt neurodegenerative diseases like Alzheimer's, Parkinson's, and Huntington's.

According to neuroscientist Mark Varney, president and CEO of Cortex, ampakines have applications far beyond Alzheimer's. The company has shown that one ampakine compound, dubbed CX717, had a positive effect on adults suffering from ADHD. This year another version of the compound will be tested for treating ADHD.



Focusing drugs influence dopamine neurotransmitters in the brain.

Preliminary studies of ampakines on healthy human subjects have shown small to moderate improvements in their performance on memory tests. "Enhancing memory may be like tuning a car that's working well," Varney says. "You can tune it only up to a certain point. In the late teens and early twenties memory is probably at its best, so you may not get much improvement. But as people get older, certain neurons die and there is reduced capacity, so these types of drugs may help."

While Cortex's drugs boost the strength of neural transmissions, another company, Helicon Therapeutics of San Diego, says it can manipulate the underlying biochemistry of memory formation. Memories are created through physical and chemical changes in synapses, the connections between brain cells that are continually remodeled in the ongoing storage and retrieval of information. That process varies depending on whether the memories are poised to be long-term or just temporary, held in place for the moment but ultimately discarded to make room for something new. If a drug could boost the transformation of short-term memory to long-term memory, it could help humans absorb and retain information with considerably less practice and commitment of time.

The key insight for building such drugs came to Tim Tully, founder and chief science officer of Helicon, when his team at Cold Spring Harbor Laboratory on Long Island stumbled upon the molecular switch: a gene called *CREB,* which is involved in converting short-term memories into long-term ones. Molecules that modulate the *CREB* pathway, increasing the gene's quantity or output, could

ZEPHYR/PHOTO RESEARCHERS

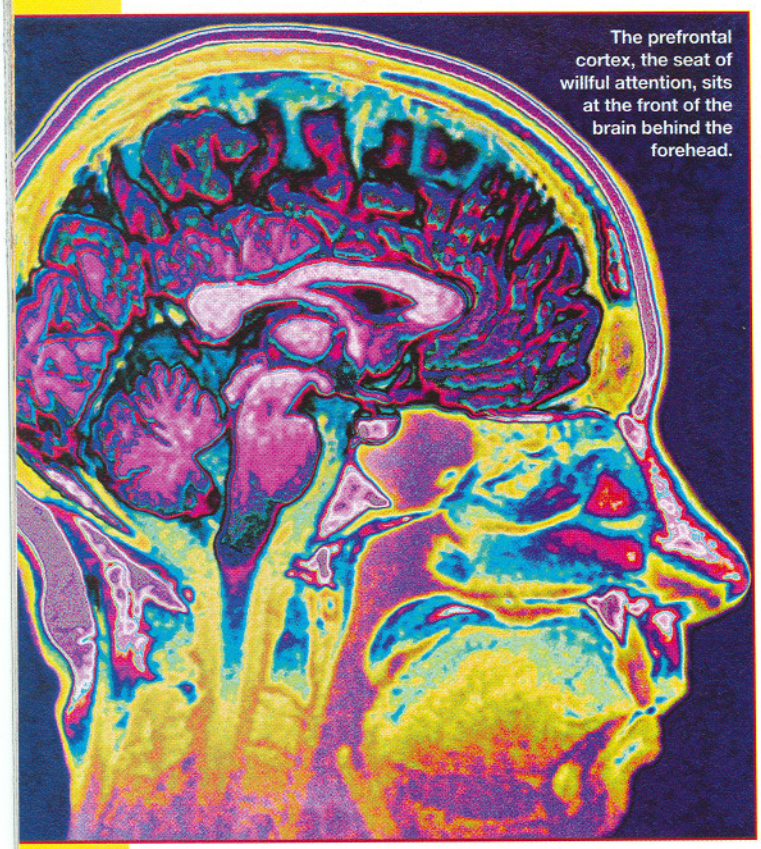
therefore be ideal memory drugs.

Helicon has since found several *CREB*-modulating compounds, experimental drugs with names like HT-0712 and HT-2157. Preliminary studies point to success. In one trial, it took monkeys only 12 days to attain a score of 85 percent accuracy on memorization tests when given the drugs, compared with 24 days to attain the same level without the drugs.

A small study in healthy humans found improvement in long-term memory there, too: Subjects were asked to try to memorize a list of 10 words and recall them seven hours later and again a week later. The researchers found that treated subjects experienced only a 2 percent loss of memory over the week, compared with a 20 percent loss for untreated controls. Helicon completed a larger human trial of the drug to test for safety in 2008 (results are not yet available) and plans another trial this year.

"These drugs reduce the amount of practice needed to commit information to long-term memory. That could make them particularly helpful in shortening the effort," Tully says.

Even successful memory enhancers may come with a downside, however. One potential problem, says psychopharmacologist Reinoud de Jongh of Erasmus University in Rotterdam, is the trade-off between long-term memory and working memory, what you hold in your brain while performing a task. For example, the prefrontal cortex (involved in working memory) and the horseshoe-shaped hippocampus (involved in long-term memory) might have opposite chemical needs. Some drugs might help keep memories fixed and thus enhance long-term storage of information. But working memory needs to be continually updated and so calls for erasure of information.



The prefrontal cortex, the seat of willful attention, sits at the front of the brain behind the forehead.

Animal studies show what can happen when a memory becomes too stable: In food-storing birds, it was possible to enhance their long-term memory for the location of their hidden food supply. When the food supply was moved, though, the birds kept searching in the old location.

Most of us have experienced the phenomenon of having a song stuck in our head. But an annoying Neil Diamond tune inexplicably playing in your brain for a while is nothing compared with reports from a handful of people who cannot forget at all.

Take the case of Jill Price, 44, who can recall minute details from every day of her life since she was 14, including what time she woke up, where she went, what she ate. Diaries she has kept since childhood show she remembers accurately, too. The condition is so rare it only recently received a label, hyperthymestic syndrome (from the Greek *thymesis,* meaning "remembering," and *hyper,* "more than normal"). Neuroscientists at the University of California at Irvine have tested Price's abilities and believe her phenomenal memory may be the result of a neurodevelopmental disorder.

Could some brain boosters cause a similar nightmare, making everything in your life unforgettable, including the most mundane parts? That could be a problem with future enhancers that aim to make it easier to learn by making long-term memories more enduring, de Jongh warns.

THAT CREATIVE SPARK

In his book *The Man Who Mistook His Wife for a Hat*, neurologist Oliver Sacks discussed a brilliant musician with Tourette's syndrome, a disease of excessive involuntary motor movements and uncontrollable impulsiveness. Treated with haloperidol, a drug that blocks dopamine from acting on receptors, the man became calm and relatively normal, but his creative jazz drive left him. Dispensing with the drug on weekends, he returned to his creative and talented, if frenetic and tic-filled, self.

In a reverse example, neurologist Ruth Walker of the James J. Peters Veterans Affairs Medical Center in New York reported the case of a Parkinson's patient who, treated with the dopamine-enhancing drug ropinirole, began producing large quantities of art. Walker wonders whether distortions in the patient's frontal lobes combined with increased stimulation of dopamine receptors could account for the increase in artistic skill. Her findings jibe with other reports that increased dopamine can lower inhibition, increase novelty seeking, and allow some people to settle into sensations—all qualities that might enhance creative drive.

These examples point to a third, broad power of mind-enhancing drugs. Experts say that some compounds, most notably psychotropics—the controversial drugs such as marijuana, LSD, mescaline, and psilocybin—can increase creativity. Reports are widespread. Experimental pharmacologist Stefano Govoni of the University of Pavia in Italy, who headed a review of cognition enhancers published in *Pharmacological Research,* points to the painter Edvard Munch, who used hallucinogenic drugs to help him produce haunting, shimmering images, including his famous work *The Scream.* Vincent van Gogh, who suffered from epilepsy, reported seeing rings around lights and halo effects as a direct result of his treatment with digitalis.

Their intoxicating effects and the fact that they are illegal hardly make hallucinogens the brain boosters of choice. But do such anecdotes make the case for safe and legal elixirs that heighten sensation and enhance creative drive? As far as the

pharmaceutical industry is concerned, apparently not. While memory and attention-boosting drugs are wending through the product pipeline, there are few signs of progress in the creative realm.

If anything, the opposite has occurred. Govoni says that when patients are treated for psychiatric disease, the creative impulses often associated with bipolar disorder, dementia, or even depression may fall by the wayside. "Many artists resist a cure in spite of the fact that they need treatment because they're concerned it may alter their creativity," he says. "Ritalin and other drugs for attention-deficit hyperactivity disorder have helped many children improve their focus and behavior. But classic ADHD traits, such as impulsivity and a disorganized life, have also been described in several thinkers, such as Albert Einstein, Salvador Dalí, Winston Churchill. What if Einstein or Churchill had taken ADHD drugs? Some researchers now wonder if would-be Einsteins and Edisons can achieve their full potential if their creativity and drive are dulled by ADHD drugs."

Drugs such as marijuana, LSD, mescaline, and psilocybin can increase creativity. But they are hardly the brain boosters of choice.

Instead of drugs, the first brain boosters to channel creativity could be electromagnetic devices designed to enhance cognitive skills. One fascinating proposal comes from Allan Snyder, director of the Centre for the Mind at the University of Sydney in Australia. He theorizes that autistic savants derive their skills from an ability to access "privileged, less processed sensory information normally inhibited from conscious awareness." For normal people, tapping that sensory well might lead to deeply buried creative riches. To test the idea, Snyder and colleagues exposed subjects to low-frequency magnetic pulses (the technology is called transcranial magnetic brain stimulation, or TMS) that suppressed part of their brain function. The researchers found that the subjects acquired savant-like skills, including the ability to render more detailed, naturalistic art.

While it may seem counterintuitive, Snyder says creativity can be enhanced by "temporarily turning off part of the brain." Our concept-driven minds fit information into known models, he explains, but "if we can turn that off, we can at least momentarily see the pattern of dots as they really are, without interpretation, and allow for a new synthesis. TMS has the potential to create creativity by removing the filters of perception and allowing people to look upon the world anew."

TRANSHUMANS

Using chemistry and technology to enhance our bodies is nothing new. Superconditioned athletes have, time and again, been tempted to dope, becoming faster and stronger with steroids and hormones that bulk up muscles—though with consequences ranging from loss of reputation to withered genitals and psychotic rage. Enhancing brains brings up similar concerns. Will cognitive tweaking have unexpected and even dangerous effects? Will it spawn a new drug culture? And is it fair for the wealthy to access a new generation of costly, off-label smart drugs while the rest of us do without?

Neuroethicist Wrye Sententia, acting director and cofounder of the nonprofit Center for Cognitive Liberty and Ethics (CCLE), responds that fears of a new drug culture à la the "tune in, turn on, drop out" 1960s just do not apply to the modern better-living-through-chemistry model. "The truth is that most of the enhancement drugs are used to enhance your performance as a worker," she says. "What's more, drugs impact different people in different ways, and in 20 years scientists will hopefully be able to provide detailed drug compatibility analyses, so safety and effectiveness will increase." Sententia also dismisses the fear of a have and have-not divide. "After all, if you look at society's technological advances, it often starts with the upper class."

Julio Licinio, a psychiatry professor and dean at the University of Miami School of Medicine, is not convinced the drugs will be so safe. He is concerned about a host of side effects from cognitive enhancement—not only the physical kind but the financial and societal, too. "Will you be at a competitive disadvantage if you don't take them?" he asks. "I have horrible jet lag when I travel and sometimes can't sleep. It is not chronic insomnia and not a disease, so I don't take drugs." But Licinio admits he has wondered how long he can hold out in the competitive world of academia when colleagues are taking Provigil, sleeping less, and gaining extra hours of work.

Perhaps the biggest proponents of enhancement are the technology boosters known as transhumanists. Their goal is the voluntary, ethical use of technology to create humans with biological capacities enhanced far beyond those of people today. Leading transhumanist Nick Bostrom, director of the University of Oxford Future of Humanity Institute, recognizes that the path may be neither fast nor direct. "The current medical system is built around preventing, diagnosing, curing, or alleviating disease," he says. "This doesn't leave enough resources for developing those mind-expanding, mind-tweaking drugs. In the short term, I'd expect things will happen as they have hitherto: by the stretching of diagnostic categories, by increasingly profligate off-label use, by people seeking their own medicines from online pharmacies. There might be exceptions carved out for particular professions—soldiers and eventually air traffic controllers and surgeons. In the longer run, some countries—perhaps Singapore, maybe China—will start to promote cognitive enhancers to their own populations, and other countries may follow suit for fear of falling behind."

As I wrap up this story, I'm preparing for a conference halfway around the world. I am stressed about deadlines and long flights and jet lag. A friend stops by and suggests I smoke a joint so I can relax. I turn down the offer. Another friend, a doctor, drops off samples of Provigil, "just in case." I also have a prescription for the antianxiety drug Klonopin in case I cannot cope with turbulence or a snoring seatmate (I'm flying in what I call Deep Vein Thrombosis Class).

At first I put the drugs aside, telling myself they aren't for me. Then I reconsider. Everything we experience has an impact on our neurobiology. I will not be exactly the same after my journey whether I take Provigil or not. But if I take the drug, it might enhance the trip by helping me focus at the conference. And is it really a less natural way to augment my life than flying 38,000 feet above the planet at 500 miles per hour? I tuck the pills into my carry-on bag and go. ■