BEHAVIOR

The Science Of Addiction

For a species wired for survival, we have an odd habit of getting hooked on things that can kill us. New research is revealing why—and opening the door to the long-dreamed-of cure

BY MICHAEL D. LEMONICK, WITH ALICE PARK

I WAS DRIVING UP THE MASSACHUSETTS Turnpike one evening last February when I knocked over a bottle of water. I grabbed for it, swerved inadvertently—and a few seconds later found myself blinking into the flashlight beam of a state trooper. "How much have you had to drink tonight, sir?" he demanded. Before I could help myself, I blurted out an answer that was surely a new one to him. "I haven't had a drink," I said indignantly, "since 1981."

It was both perfectly true and very pertinent to the trip I was making. By the time I reached my late 20s, I'd poured down as much alcohol as normal people consume in a lifetime and plenty of drugs—mostly pot—as well. I was, by any reasonable measure, an active alcoholic. Fortunately, with a lot of help, I was able to stop. And now I was on my way to McLean Hospital in Belmont, Massachusetts, to have my brain scanned in a functional magnetic-resonance imager (fMRI). The idea was to see what the inside of my head looked like after more than a quarter-century on the wagon.

Back when I stopped drinking, such an experiment would have been unimaginable. At the time, the medical establishment had come to accept the idea that alcoholism was a disease rather than a moral failing; the American Medical Association (AMA) had said so in 1950. But while it had all the hallmarks of other diseases, including specific symptoms and a predictable course, leading to disability or even death, alcoholism was different. Its physical basis was a complete mystery—and since nobody forced alcoholics to drink, it was still seen, no matter what the AMA said, as somehow voluntary. Treatment consisted mostly of talk therapy, maybe some vitamins and usually a strong recommendation to join Alcoholics Anonymous. Although it's a totally nonprofessional organization, founded in 1935 by an ex-drunk and an active drinker, AA has managed to get millions of people off the bottle, using group support and a program of accumulated folk wisdom.

While AA is astonishingly effective for some people, it doesn't work for everyone; studies suggest it succeeds about 20% of the time, and other forms of treatment, including various types of behavioral therapy, do no better. The rate is much the same with drug addiction, which experts see as the same disorder triggered by a different chemical. "The sad part is that if you look at where addiction treatment was 10 years ago, it hasn't gotten much better," says Dr. Martin Paulus, a professor of psychiatry at the University of California at San Diego. "You have a better chance to do well after many types of cancer than you have of recovering from methamphetamine dependence."

Addiction is so harmful, evolution should have weeded it out by now. If it's hard to drive under the influence, imagine running from a tiger

That could all be about to change. During those same 10 years, researchers have made extraordinary progress in understanding the physical basis of addiction. They know now, for example, that the 20% success rate can shoot up to 40% if treatment is ongoing (very much the AA model, which is most effective when members continue to attend meetings long after their last drink). Armed with an array of increasingly sophisticated technology, including fMRIs and PET scans, investigators have begun to figure out exactly what goes wrong in the brain of an addict—which neurotransmitting chemicals are out of balance and what regions of the brain are affected. They are developing a more detailed understanding of how deeply and completely addiction can affect the brain, by hijacking memory-making processes and by exploiting emotions. Using that knowledge, they've begun to design new drugs that are showing promise in cutting off the craving that drives an addict irresistibly toward relapse—the greatest risk facing even the most dedicated abstainer.

"Addictions," says Joseph Frascella, director of the division of clinical neuroscience at the U.S. National Institute on Drug Abuse (NIDA), "are repetitive behaviors in the face of negative consequences, the desire to con-

PHOTO-ILLUSTRATION BY ARTHUR HOCHSTEIN (BRAIN SCAN—GETTY; GLASS—STOCKFOOD)

tinue something you know is bad for you."

Addiction is such a harmful behavior, in fact, that evolution should have long ago weeded it out of the population: if it's hard to drive safely under the influence, imagine trying to run from a saber-toothed tiger or catch a squirrel for lunch. And yet, says Dr. Nora Volkow, director of NIDA and a pioneer in the use of imaging to understand addiction, "the use of drugs has been recorded since the beginning of civilization. Humans in my view will always want to experiment with things to make them feel good."

That's because drugs of abuse co-opt the very brain functions that allowed our distant ancestors to survive in a hostile world. Our minds are programmed to pay extra attention to what neurologists call salience—that is, special relevance. Threats, for example, are highly salient, which is why we instinctively try to get away from them. But so are food and sex because they help the individual and the species survive. Drugs of abuse capitalize on this ready-made programming. When exposed to drugs, our memory systems, reward circuits, decision-making skills and conditioning kick in—salience in overdrive—to create an all consuming pattern of uncontrollable craving. "Some people have a genetic predisposition to addiction," says Volkow. "But because it involves these basic brain functions, everyone will become an addict if sufficiently exposed to drugs or alcohol."

In the brains of addicts, there is reduced activity in the prefrontal cortex, where rational thought can override impulsive behavior

That can go for nonchemical addictions as well. Behaviors, from gambling to shopping to sex, may start out as habits but slide into addictions. Sometimes there might be a behavior-specific root of the problem. Volkow's research group, for example, has shown that pathologically obese people who are compulsive eaters exhibit hyperactivity in the areas of the brain that process food stimuli—including the mouth, lips and tongue. For them, activating these regions is like opening the floodgates to the pleasure center. Almost anything deeply enjoyable can turn into an addiction, though.

Of course, not everyone becomes an addict. That's because we have other, more analytical regions that can evaluate con-

What Hooks Us. Addictions in America change over time. Here's a look at what we're battling now

Substance and behavioral addictions

Alcohol

About **18.7 million** people, or 7.7% of the population, are dependent on or abuse alcohol, and **12,000 more** try it for the first time every day. Alcoholics Anonymous has 2 million members—impressive, but only a small fraction of those who need help.

Drugs

An estimated **3.6 million** people are dependent on drugs. On average, 8,000 try them for the first time each day, and 700,000 are undergoing treatment for addiction. **More than half** of first-time users are female and younger than 18. Marijuana, cocaine and pain relievers are the leading drugs of abuse.

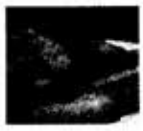
Tobacco

There are about **71.5 million** users of tobacco products in the U.S. About **23.4%** of men and **18.5%** of women are cigarette smokers, with cigarette use lowest in Western states and highest in the Midwest; 44.3% of young adults ages 18 to 25 use tobacco, the highest rate for any age group.

Caffeine

It's the most widely used mood-altering drug in the world and is routinely ingested by about **80% to 90%** of Americans, primarily through soda and coffee. A daily brewed cup of joe, with 100 mg of caffeine, can lead to physical dependence. Withdrawal symptoms are experienced by **40% to 70%** of those trying to quit.

Food



An addiction to food affects as many as **4 million** U.S. adults and is strongly linked to depression. About **15%** of mildly obese people are compulsive eaters. Binge eating, thought to be the most common eating disorder in America, is considered bulimia when a person purges to lose weight.

Gambling

Two million American adults, or 0.67% of the population, are thought to be pathological gamblers, wagering heedless of the consequences. Their moods generally follow the arc of their winning and losing. An additional **4 million to 8 million** are considered problem gamblers.

Shopping

At least **1 in 20** Americans is a compulsive shopper, according to a Stanford University study. The addiction affects both genders almost equally. Cultural factors, like advertising's emphasis on the happiness products can bring, are thought to fuel addictive buying.

Sex

About **16 million** Americans suffer from compulsive sexual behavior, the least understood of all addictions. A third are women; about **60%** of all sex addicts were abused in childhood. An addict is dependent on the neurochemical changes that take place during sex and is consumed by sexual thoughts.

Internet

Like compulsive gambling, Internet addiction is thought to be an **impulse-control disorder** that can disrupt social relationships. There is disagreement as to whether it should be formally considered a disorder. Though substance abusers strive for abstinence, an Internet addict's goal is often to attain moderation.

PHOTOS, FROM TOP: JUPITERIMAGES (3); ISTOCKPHOTO (2); JUPITERIMAGES (2); ISTOCKPHOTO (2)

Sources: Department of Health and Human Services, SAMHSA Office of Applied Studies 2006 National Survey on Drug Use and Health (ages 12 years and old); American Heart Association; Johns Hopkins University study, Principles of Addiction Medicine; Psychology Today; National Gambling Impact Commission Study; National Council on Problem Gambling; Illinois Institute for Addiction Recovery; Society for Advancement of Sexual Health; APsych Journal

Addiction timeline

1400 | 1450 | 1500 | 1550 | 1600 | 1650 | 1700 | 1750 | 1800 | 1850 | 00

3000 B.C. Evidence of first wine industry along the banks of the Nile

1492 Columbus travels to the West Indies and sees Native Americans smoking tobacco

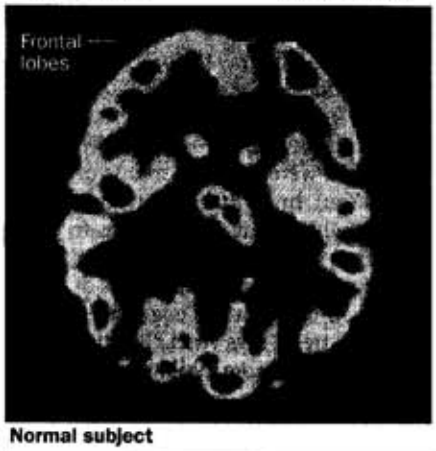
1600 Marijuana cultivation begins in the U.S. with the Jamestown settlers, who used its strong fibers to make ropes and clothing

The brain of an addict

Cocaine use causes a decrease in glucose metabolism in the brain, especially in the frontal lobes, where planning, abstract thinking and regulation of impulse behavior are governed.

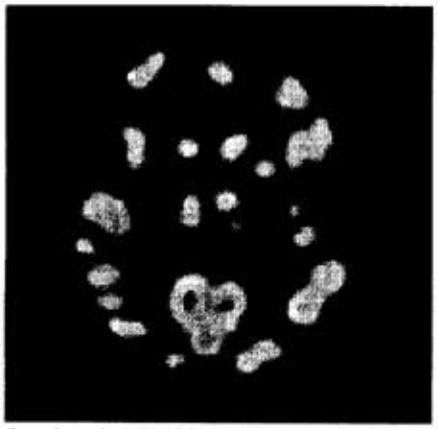
Glucose metabolism

Lower activity — Higher activity



Normal subject

Cocaine abuser 10 days after abuse stops

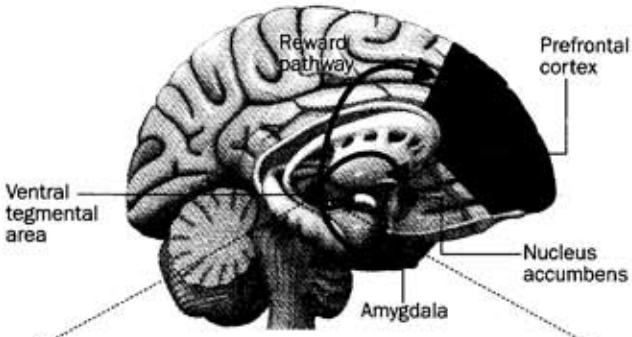


Cocaine abuser 100 days after abuse stops

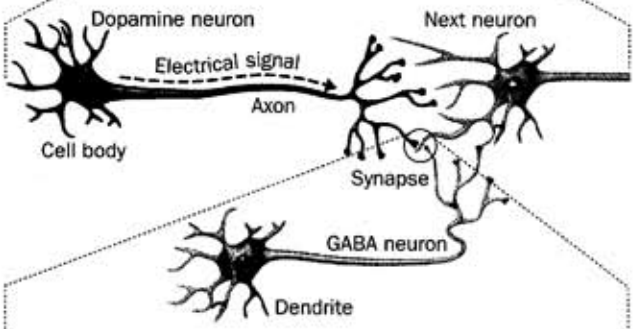
BRAINS SCANS: COURTESY NIH/NIDA (3)

What happens in the brain

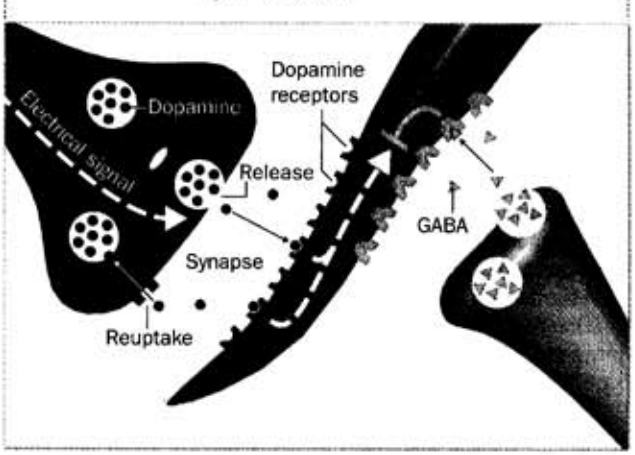
1. We feel good when neurons in the reward pathway release a neurotransmitter called dopamine into the nucleus accumbens and other brain areas.



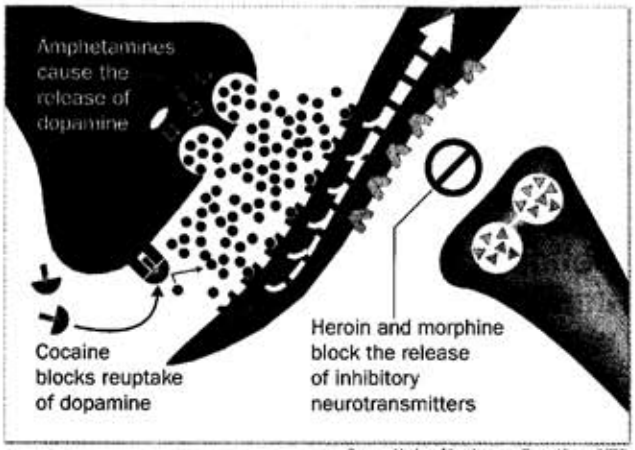
2. Neurons in the reward pathway communicate by sending electrical signals down their axons. The signal is passed to the next neuron across a small gap called the synapse.



3. Dopamine is released into the synapse, crosses to the next neuron and binds to receptors, providing a jolt of pleasure. Excess dopamine is taken back up by the sending cell. Other nerve cells release GABA, an inhibitory neurotransmitter that works to prevent the receptor nerve from being overstimulated.



4. Addictive substances increase the amount of dopamine in the synapse, heightening the feeling of pleasure. Addiction occurs when repeated drug use disrupts the normal balance of brain circuits that control rewards, memory and cognition, ultimately leading to compulsive drug taking.



Source: National Institute on Drug Abuse (NIH)
TIME Diagram by Kristina Dell, Meg Massey and Joe Lertola

1910 1920 1930 1940 1950 1960 1970 1980 1990 2000

1830 Alcohol addiction is rampant in Britain, owing in part to industrialization

1919 National Prohibition Act in effect to decrease alcohol consumption

1935 A stockbroker and a surgeon begin Alcoholics Anonymous

1971 President Richard Nixon declares a "war on drugs"

1982 U.S. cocaine use peaks, with 10.4 million users

1985 Crack cocaine first appears in large cities like Miami and New York

1994 Tobacco industry denies nicotine is addictive

sequences and override mere pleasure seeking. Brain imaging is showing exactly how that happens. Paulus, for example, looked at methamphetamine addicts enrolled in a military veterans hospital's intensive four-week rehabilitation program. Those who were more likely to relapse in the first year after completing the program were also less able to complete tasks involving cognitive skills and less able to adjust to new rules quickly. This suggested that those patients might also be less adept at using analytical areas of the brain while performing decision-making tasks. Indeed, brain scans showed that there were reduced levels of activation in the prefrontal cortex, where rational thought can override impulsive behavior. It's impossible to say if the drugs might have damaged these abilities in the relapsers—an effect rather than a cause of the chemical abuse—but the fact that the cognitive deficit existed in only some of the meth users suggests that there was something innate that was unique to them. To his surprise, Paulus found that 80% to 90% of the time, he could accurately predict who would relapse within a year simply by examining the scans.

Another area of focus for researchers involves the brain's reward system, powered largely by the neurotransmitter dopamine. Investigators are looking specifically at the family of dopamine receptors that populate nerve cells and bind to the compound. The hope is that if you can dampen the effect of the brain chemical that carries the pleasurable signal, you can loosen the drug's hold.

One particular group of dopamine receptors, for example, called D3, seems to multiply in the presence of cocaine, methamphetamine and nicotine, making it possible for more of the drug to enter and activate nerve cells. "Receptor density is thought to be an amplifier," says Frank Vocci, director of pharmacotherapies at NIDA. "[Chemically] blocking D3 interrupts an awful lot of the drugs' effects. It is probably the hottest target in modulating the reward system."

But just as there are two ways to stop a speeding car—by easing off the gas or hitting the brake pedal—there are two different possibilities for muting addiction. If dopamine receptors are the gas, the brain's own inhibitory systems act as the brakes. In addicts, this natural damping circuit, called GABA (gamma-aminobutyric acid), appears to be faulty. Without a proper chemical check on excitatory messages set off by drugs, the brain never appreciates that it's been satiated.

As it turns out, vigabatrin, an anti-epilepsy treatment that is marketed in 60 countries (but not yet in the U.S.), is an effective GABA booster. In epileptics, vigabatrin suppresses overactivated motor neurons that cause muscles to contract and go into spasm. Hoping that enhancing GABA in the brains of addicts could help them control their drug cravings, two biotech companies in the U.S., Ovation Pharmaceuticals and Catalyst Pharmaceuticals, are studying the drug's effect on methamphetamine and cocaine use. So far, in animals, vigabatrin prevents the breakdown of GABA so that more of the inhibitory compound can be stored in whole form in nerve cells. That way, more of it could be released when those cells are activated by a hit from a drug. Says Vocci, optimistically: "If it works, it will probably work on all addictions."

Another fundamental target for addiction treatments is the stress network. Animal studies have long shown that stress can increase the desire for drugs. In rats trained to self-administer a substance, stressors such as a new environment, an unfamiliar cage mate or a change in daily routine push the animals to depend on the substance even more.

Among higher creatures like us, stress can also alter the way the brain thinks, particularly the way it contemplates the consequences of actions. Recall the last time you found yourself in a stressful situation—when you were scared, nervous or threatened. Your brain tuned out everything besides whatever it was that was frightening you—the familiar fight-or-flight mode. "The part of the prefrontal cortex that is involved in deliberative cognition is shut down by stress," says Vocci. "It's supposed to be, but it's even more inhibited in substance abusers." A less responsive prefrontal cortex sets up addicts to be more impulsive as well.

Hormones—of the male-female kind—may play a role in how people become addicted as well. Studies have shown, for instance, that women may be more vulnerable to cravings for nicotine during the latter part of the menstrual cycle, when the egg emerges from the follicle and the hormones progesterone and estrogen are released. "The reward systems of the brain have different sensitivities at different points in the cycle," notes Volkow. "There is way greater craving during the later phase."

That led researchers to wonder about other biological differences in the way men

ad•dic•tion

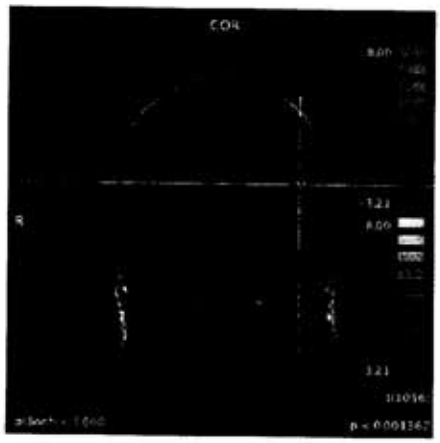
Defining addiction can seem as hard as fixing it. What separates a heavy user from a problem user from an addict? Four experts offer answers

'Addiction has a specific definition: you are unable to stop when you want to, despite [being] aware of the adverse consequences. It permeates your life; you spend more time satisfying [your craving].'

—DR. NORA VOLKOW, DIRECTOR, U.S. NATIONAL INSTITUTE ON DRUG ABUSE

'Addiction is not just about substances. Addiction is about disrupting the processing of pleasure; the balance point is shifted so you keep creating more and more urges, and you keep wanting more and more.'

—DR. MARTIN PAULUS, PROFESSOR OF PSYCHIATRY, UNIVERSITY OF CALIFORNIA, SAN DIEGO



All quiet *After 26 years of sobriety, the author's brain did not react to cues that would cause an active alcoholic's brain to light up with activity.*

and women become addicted and, significantly, respond to treatments. Alcohol dependence is one very promising area. For years, researchers had documented the way female alcoholics tend to progress more rapidly to alcoholism than men. This telescoping effect, they now know, has a lot to do with the way women metabolize alcohol. Females are endowed with less alcohol dehydrogenase—the first enzyme in the stomach lining that starts to break down the ethanol in liquor—and less total body water than men. Together with estrogen, these factors have a net concentrating effect on the alcohol in the blood, giving women a more intense hit with each drink. The pleasure from that extreme high may be enough for some women to feel satisfied and therefore drink less. For others, the intense intoxication is so enjoyable that they try to duplicate the experience over and over.

But it's the brain, not the gut, that continues to get most of the attention, and one of the biggest reasons is technology. It was in 1985 that Volkow first began using PET scans to record trademark characteristics in the brains and nerve cells of chronic drug abusers, including blood flow, dopamine levels and glucose metabolism—a measure of how much energy is being used and where (and therefore a stand-in for figuring out which cells are at work). After the subjects had been abstinent a year, Volkow rescanned their brains and found that they had begun to return to their predrug state. Good news, certainly, but only as far as it goes.

"The changes induced by addiction do not just involve one system," says Volkow. "There are some areas in which the changes persist even after two years." One area of delayed rebound involves learning. Somehow in methamphetamine abusers, the ability to learn some new things remained affected after 14 months of abstinence. "Does treatment push the brain back to normal," asks NIDA's Frascella, "or does it push it back in different ways?"

If the kind of damage that lingers in an addict's learning abilities also hangs on in behavioral areas, this could explain why rehabilitation programs that rely on cognitive therapy—teaching new ways to think about the need for a substance and the consequences of using it—may not always be effective, especially in the first weeks and months after getting clean. "Therapy is a learning process," notes Vocci. "We are trying to get [addicts] to change cognition and behavior at a time when they are least able to do so."

One important discovery: evidence is building to support the 90-day rehabilitation model, which was stumbled upon by AA (new members are advised to attend a meeting a day for the first 90 days) and is the duration of a typical stint in a drug-treatment program. It turns out that this is just about how long it takes for the brain to reset itself and shake off the immediate influence of a drug. Researchers at Yale University have documented what they call the sleeper effect—a gradual re-engaging of proper decision making and analytical functions in the brain's prefrontal cortex—after an addict has abstained for at least 90 days.

This work has led to research on cognitive enhancers, or compounds that may amplify connections in the prefrontal cortex to speed up the natural reversal. Such enhancement would give the higher regions of the brain a fighting chance against the amygdala, a more basal region that plays a role in priming the dopamine-reward system when certain cues suggest imminent pleasure—anything from the sight of white powder that looks like cocaine to spending time with friends you used to drink with. It's that conditioned reflex—identical to the one that caused Ivan Pavlov's famed dog to salivate at the ringing of a bell after it learned to associate the sound with food—that unleashes a craving. And it's that phenomenon that was the purpose of my brain scans at McLean, one of the world's premier centers for addiction research.

In my heyday, I would often drink even when I knew it was a terrible idea—and the urge was hardest to resist when I was with my drinking buddies, hearing the clink of glasses and bottles, seeing others imbibe and smelling the aroma of wine or beer. The researchers at McLean have invented a machine that wafts such odors directly into the nostrils of a subject undergoing an FMRI scan in order to see how the brain reacts. The reward circuitry in the brain of a newly recovering alcoholic should light up like a Christmas tree when stimulated by one of these alluring smells.

I chose dark beer, my absolute favorite, from their impressive stock. But I haven't gotten high for more than a quarter-century; it was an open question whether I would react that way. So after an interview with a staff psychiatrist to make sure I would be able to handle it if I experienced a craving, I was fitted with a tube that carried beer aroma from a vaporizer into my nose. I was then slid into the machine to inhale that still

FROM LEFT: BRIAN FINKE—LEVINE & LEAVITT FOR TIME; ADRIANA BORNSCHLOCK—MCLEAN HOSPITAL

'Addiction is a chronic and relapsing brain disease characterized by uncontrollable drug-seeking behavior and use. It persists even with the knowledge of negative health and social consequences.'
—SCOTT LUKAS, MCLEAN HOSPITAL

'Addictions occur when behaviors start to become excessive. They are driven by our systems that stand up, shake us and say, "The brain is saying this is good; we should do it again."'
—JOSEPH FRASCELLA, DIRECTOR, CLINICAL NEUROSCIENCE, NIDA

Addicts in Art and Life

Addiction has always been the stuff of drama, both on the screen and in the lives of the privileged and famous

THE ICONS

Drugs, drink and fame *Addiction victims, clockwise from left: Kurt Cobain, Marilyn Monroe, Jimi Hendrix, Betty Ford, Sid Vicious, Billie Holiday, artist Jean-Michel Basquiat, Edie Sedgwick (actress in Andy Warhol films), W.C. Fields*

THE MOVIES

***The Man with the Golden Arm*, 1955** *Frank Sinatra as a heroin addict*

***Valley of the Dolls*, 1967** *Patty Duke struggles with pills—nicknamed dolls*

***Less Than Zero*, 1987** *Robert Downey Jr., addicted onscreen and in real life*

***Requiem for a Dream*, 2000** *Jennifer Connelly faces heroin, pills and despair*

familiar odor while the fMRI did its work.

Even if the smells triggered a strong desire to drink, I had long since learned ways to talk myself out of it—or find someone to help me do so. Like the 90-day drying-out period that turns out to parallel the brain's recovery cycle, such a strategy is in line with other new theories of addiction. Scientists say extinguishing urges is not a matter of getting the feelings to fade but of helping the addict learn a new form of conditioning, one that allows the brain's cognitive power to shout down the amygdala and other lower regions. "What has to happen for that cue to extinguish is not for the amygdala to become weaker but for the frontal cortex to become stronger," says Vocci.

While such relearning has not been studied formally in humans, Vocci believes it will work, on the basis of studies involving, of all things, phobias. It turns out that phobias and drugs exploit the same struggle between high and low circuits in the brain. People placed in a virtual-reality glass elevator and treated with the antibiotic D-cycloserine were better able to overcome their fear of heights than those without benefit of the drug. Says Vocci: "I never thought we would have drugs that affect cognition in such a specific way."

Such surprises have even allowed experts to speculate whether addiction can ever be cured. That notion goes firmly against current beliefs. A rehabilitated addict is always in recovery because *cured* suggests that resuming drinking or smoking or shooting up is a safe possibility—whose downside could be devastating. But there are hints that a cure might not in principle be impossible. A recent study showed that tobacco smokers who suffered a stroke that damaged the insula (a region of the brain involved in emotional, gut-instinct perceptions) no longer felt a desire for nicotine.

That's exciting, but because the insula is so critical to other brain functions—perceiving danger, anticipating threats—damaging this area isn't something you would ever want to do intentionally. With so many of the brain's systems entangled with one another, it could prove impossible to adjust just one without throwing the others into imbalance.

Nevertheless, says Volkow, "addiction is a medical condition. We have to recognize that medications can reverse the pathology of the disease. We have to force ourselves to think about a cure because if we don't, it will never happen." Still, she is quick to admit that just contemplating new ideas doesn't make them so. The brain functions that addiction commandeers may simply be so complex that sufferers, as 12-step recovery programs have emphasized for decades, never lose their vulnerability to their drug of choice, no matter how healthy their brains might eventually look.

I'm probably a case in point. My brain barely lit up in response to the smell of beer inside the fMRI at McLean. "This is actually valuable information for you as an individual," said Scott Lukas, director of the hospital's behavioral psychopharmacology research laboratory and a professor at Harvard Medical School who ran the tests. "It means that your brain's sensitivity to beer cues has long passed."

That's in keeping with my real-world experience; if someone has a beer at dinner, I don't feel a compulsion to leap across the table and grab it or even to order one for myself. Does that mean I'm cured? Maybe. But it may also mean simply that it would take a much stronger trigger for me to fall prey to addiction again—like, for example, downing a glass of beer. But the last thing I intend to do is put it to the test. I've seen too many others try it—with horrifying results. ■