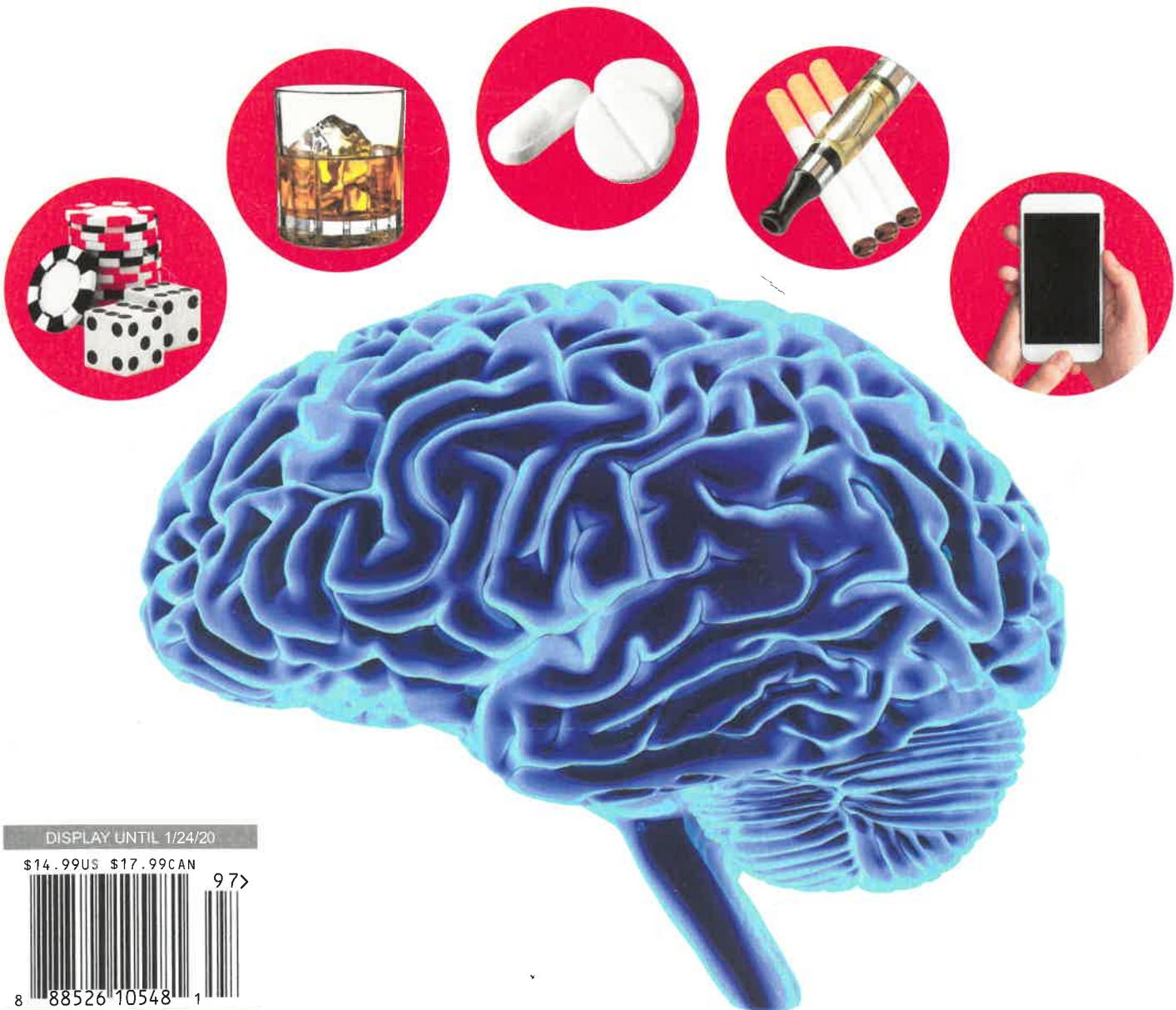
SPECIAL **TIME** EDITION

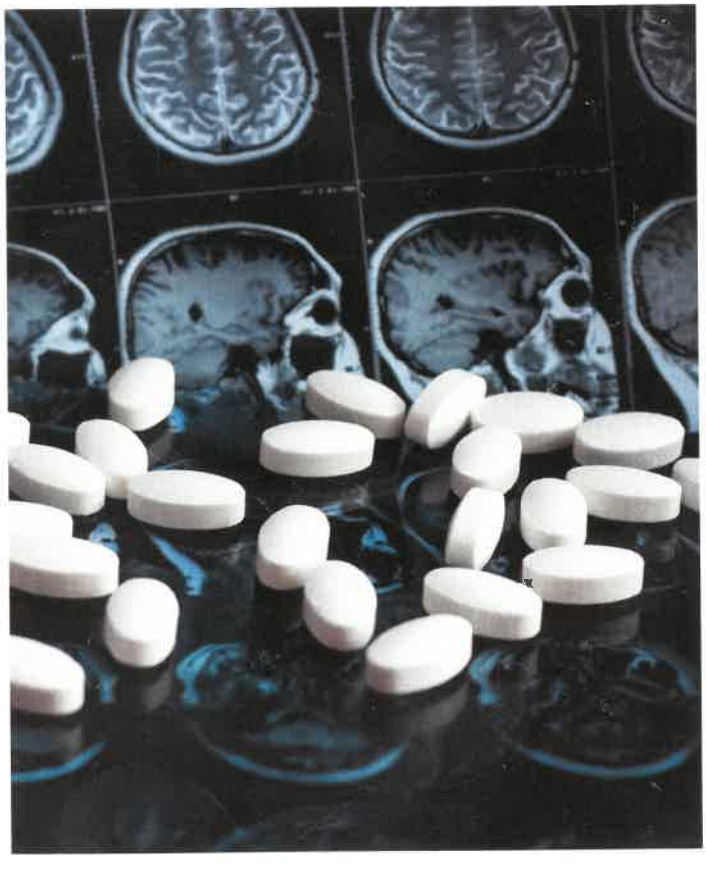
THE SCIENCE OF ADDICTION

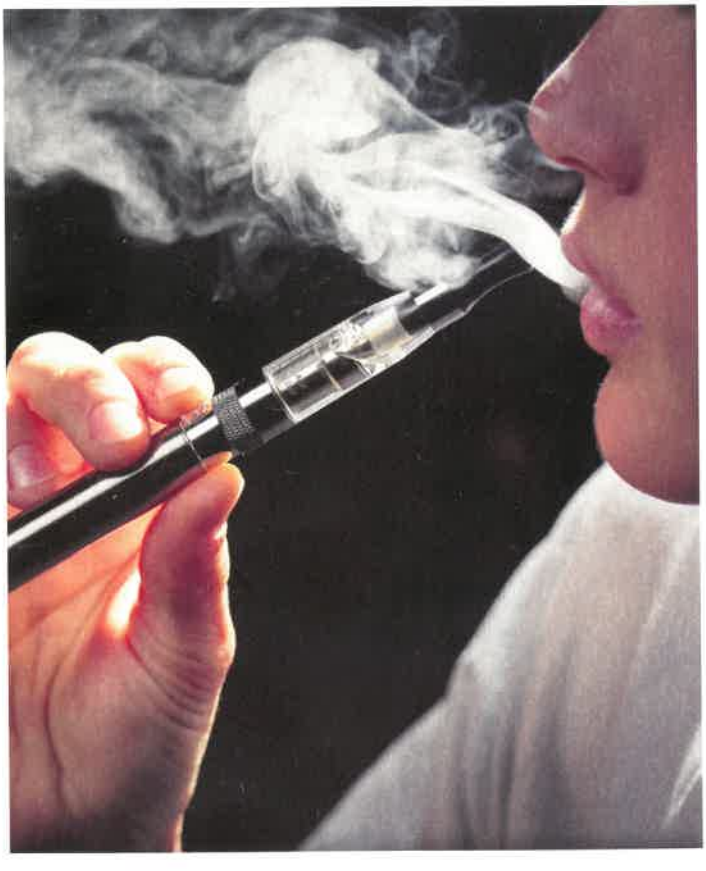
What We Know. What We're Learning.

CONFRONTING AN EPIDEMIC | **SUPPORTING LOVED ONES** | **TREATMENT AND HOPE**



The rise in addictions has had an impact on so many lives and families. It has also led to a rise in knowledge, compassion and hope.





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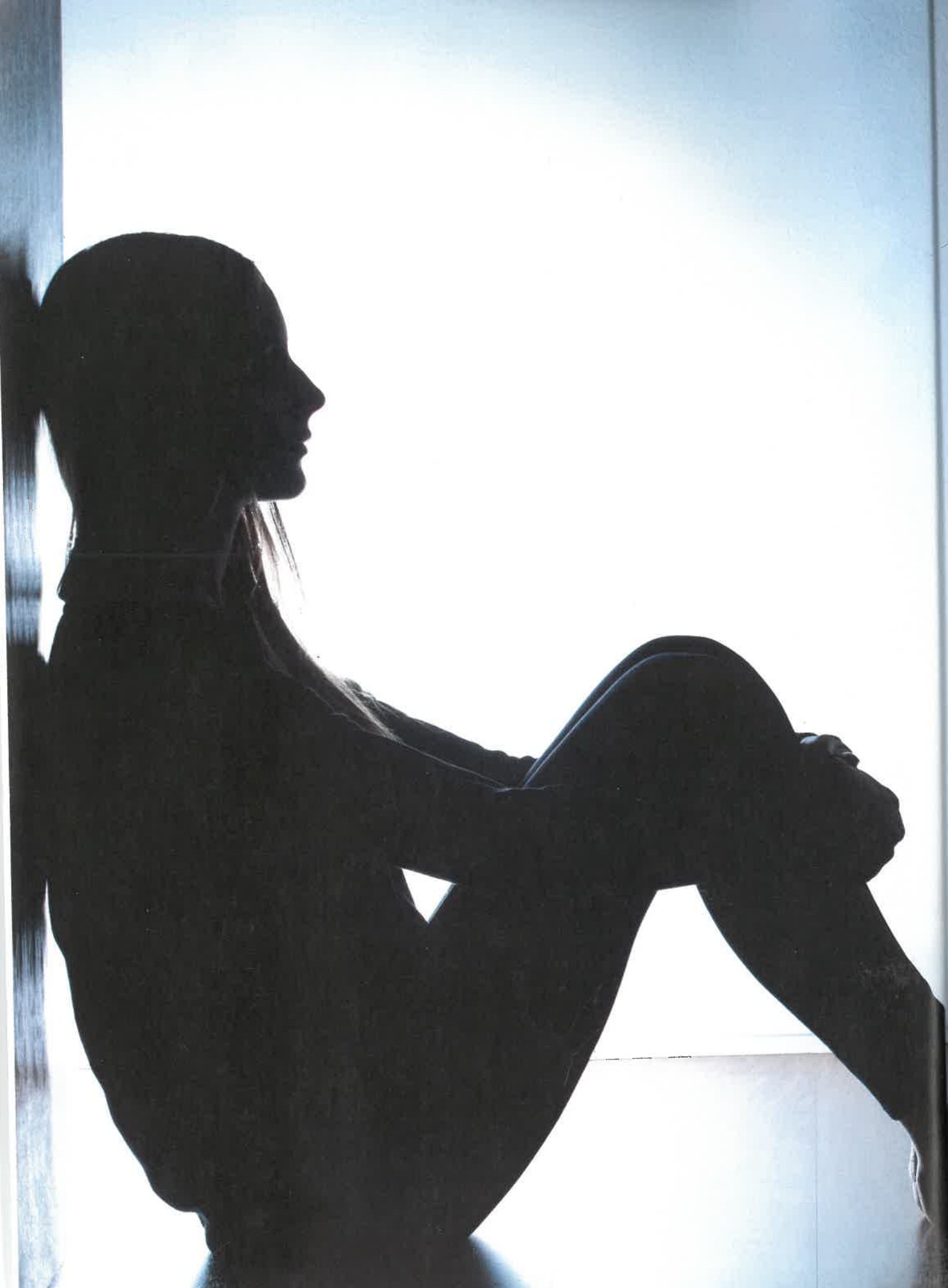

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Parts of this edition appeared previously in TIME and *Money*.

THE DISEASE OF THE PLEASURES

For as long as human beings have had ways to feel good, we've struggled to know when it's time to stop. By Jeffrey Kluger

YOUR BRAIN IS VERY SIMPLEMINDED—AND SO IS everyone else's. That's not the way we think of ourselves, of course. Great minds have produced great works over the long arc of human history—breakthroughs in art, science, engineering, exploration—and it takes no small amount of genius to accomplish so much.

But thinking big thoughts is only a fraction of what our brains do. Much of the rest is pretty primal stuff—regulating breathing, managing memory, interpreting sight and sound and touch and taste. It's the brain that puts us to sleep at night and runs the interior cinema that is our dreams.

The brain does another thing too: it processes pleasure—the satisfaction of eating; the thrill of sex; the exhilaration of winning; the light, loopy, all-is-well feeling of being buzzed on drink or drugs. It's all just chemistry, this or that neurotransmitter engaging this or that receptor, sending a crackle of happiness along neuronal circuits that never knew such joy before the first time you downed a glass of beer or won a hand of poker or took a little opioid. You'd heard other people describe the experiences, and now that you've had them yourself, you'd sure like to do it all again. And then again. And yet again. And that's where things can go awry.

There's a gravity to temptation, an attractive force that overcomes the friction of your resistance. There is not a person who ever cheated on a spouse who didn't feel that implacable pull, accelerating faster and faster toward the object of desire with the internal voice that counsels discipline, fidelity, the sanctity of the marriage vows getting fainter and fainter as it is left further and further behind. There's not a person who had a third or fifth or 10th drink, or gambled away the last dollar of this week's paycheck, or ate a second pint of ice cream who didn't surrender to the same inexorable power.

Sometimes we learn from those lost battles, with the hangover or the numbers on the scale or the heartbreak of a spouse being enough to set us right. Sometimes, however, there is no lesson learned, or at least no lesson heeded. Sometimes instead we're powerless to *not* repeat the behavior. Perhaps we intend to behave—we *promise* ourselves and the other people in our world that we'll behave—but always we fail. The behavior becomes a habit, the habit becomes a compulsion, and the compulsion becomes the life-wrecking disease that is addiction.

The numbers are scary enough. The U.S. is in the midst of an epidemic of opioid addiction unlike any health crisis the nation has ever faced. In 2017, more

than 47,000 Americans died of opioid overdoses. At this point, an average of 130 are claimed by the drugs every day. Up to 29% of people who are prescribed opioids for chronic pain wind up misusing them.

And opioids are hardly the only class of chemical that's taking such an awful toll. More than 20 million Americans 12 and older had some kind of substance-abuse disorder in 2018, according to the National Survey on Drug Use and Health. One out of every eight adults is simultaneously battling both alcohol and drug misuse. And among Americans with mental-health disorders, 9.2 million also have a substance-abuse problem—perhaps seeking relief from emotional pain in alcohol or pills, perhaps pushed toward the intoxicants by a simple lack of impulse control, which can be a symptom of mental-health conditions such as oppositional defiant disorder. Either way, they suffer doubly.

Chemicals, of course, are not the only things that can draw us in and seize our will. The concept of behavioral addictions—to sex, online gaming, pornography, gambling, shopping and food—is controversial among addiction specialists; however, brain scans of problem gamblers show the same regions lighting up in the same way that alcohol and drug cravings do in an addicted person, driving the same cycle of craving, bingeing, remorse and repeat.

SOMETIMES WE'RE POWERLESS TO *NOT* REPEAT THE BEHAVIOR.

No one knows the exact cause of addictions, why some people are claimed by them while others can thread the needle of enjoying some indulgences but pulling up short before some becomes too much. Genes surely play a role, with studies showing, for example, that identical twins are far likelier to share addictions than fraternal twins. And availability matters. There are few shopping addicts in impoverished communities, few alcoholics in dry countries.

Treatment and recovery differ from person to person, but experts agree that it should be multifaceted and ongoing. Medications can help; the 12-step model works; even the surgical intervention of deep brain stimulation may have a place. What is consistent among addicted people from era to era has been the groping for a cure, the desperation to turn the brain back to a seat of pleasure again. There are answers, but there is much darkness to endure before the light breaks again. ◻

CHAPTER 1

The Addi

The causes of addiction, much like the individuals it affects, are complexly unique. But from behavioral fixations to chemical compulsions, answers may lie in our brains, our genes and the greater world around us.

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THE SCIENCE OF ADDICTION

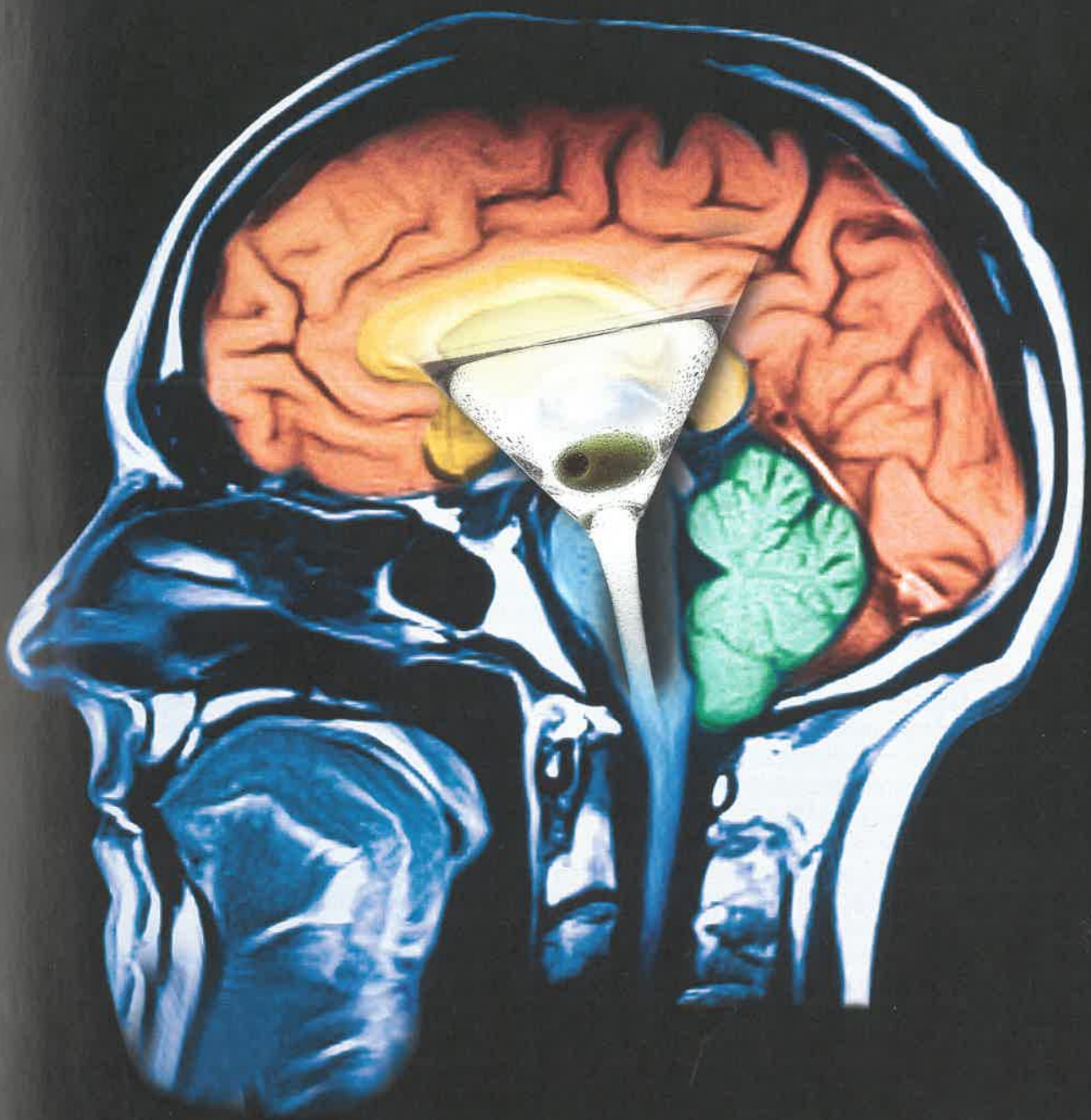
For a species wired for survival, we have an odd habit of getting hooked on things that can kill us. New research is revealing why—and opening the door to the long-dreamed-of cure. By Michael D. Lemonick

I WAS DRIVING UP THE MASSACHUSETTS TURNpike one evening many years ago 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, Mass., 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 1956. 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.

Although AA is astonishingly effective for some people, it doesn't work for everyone; studies about its success rate vary wildly from 5% to 50%, but many fall around 10%. Other forms of treatment, including various types of behavioral therapy, don't even do that well. The rate is no better 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 years ago, it hasn't gotten much better," says Martin Paulus, a former professor of psychiatry at the University of California, San Diego, and now president of the Laureate Institute for Brain Research



Scientists have begun using fMRIs and PET scans to study how addiction can affect the brain.

in Tulsa, Okla. "You have a better chance to do well after many types of cancer than you have of recovering from methamphetamine dependence."

That could change. In recent years, researchers have made extraordinary progress in understanding the physical basis of addiction. They know now, for example, that success rates can shoot up to 60% 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 could cut off the craving that drives an addict irresistibly toward relapse—the greatest risk facing even the most dedicated abstainer.

Addiction is defined as a chronic relapsing behavior in the face of negative consequences; the overwhelming urge to continue something you know is bad for you. It is such a harmful behavior, in fact, that evolution should have long ago weeded addiction 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," points out Nora Volkow, director of the National Institute on Drug Abuse (NIDA) at the National Institutes of Health 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—

Nora Volkow, director of the National Institute on Drug Abuse, studies the neurological roots of addiction.

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 addicted person if sufficiently exposed to drugs or alcohol."

That can go for nonchemical addictions as well. Behaviors, from gambling to shopping to sex, may start out as habits but slide into compulsions. 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 has the potential to become addictive, though.

Of course, not everyone becomes addicted. That's because we have other, more analytical regions that can evaluate consequences and override mere pleasure-seeking. Brain imaging is showing exactly how that happens. Paulus, for example, looked

at people addicted to methamphetamine who were enrolled in a VA 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. Sure enough, 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.

ALMOST ANYTHING DEEPLY ENJOYABLE HAS THE POTENTIAL TO BE ADDICTIVE.

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, formerly with NIDA and now president of the Friends Research Institute in Baltimore. "[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 people with addictions, 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 antiepilepsy treatment, is an effective GABA booster. In epileptics, vigabatrin suppresses overactivated motor neurons that cause muscles to contract and go into spasm. 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 can be released when those cells are activated by a hit from a drug. Biotech companies in the U.S. have been researching the drug's effect on cocaine and alcohol use, in the hopes that enhancing GABA in the brains of addicted persons would help control their cravings. Preclinical evidence suggests the drug may be effective in reducing cocaine and alcohol intake.

Another fundamental target for addiction treatments is the stress network. Animal studies show 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 routine lead to more substance use.

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 chronic substance users." A less responsive prefrontal cortex sets up people with addictions to be more impulsive as well.

Sex hormones may also play a role in how people become addicted. 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 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 and women become addicted and, significantly, respond to treat-

ments. 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 do. This telescoping effect, they now know, has a lot to do with the way women metabolize alcohol. Females produce 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 users, 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 pre-drug state. Good news, certainly, but only as far as it goes.

THERE ARE HINTS THAT A CURE MIGHT NOT IN PRINCIPLE BE IMPOSSIBLE.

"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 chronic methamphetamine users, the ability to learn some new things remained affected after 14 months of abstinence. "Does treatment push the brain back to normal," asks Joseph Frascella, a senior science adviser for NIDA, "or does it push it back in different ways?"

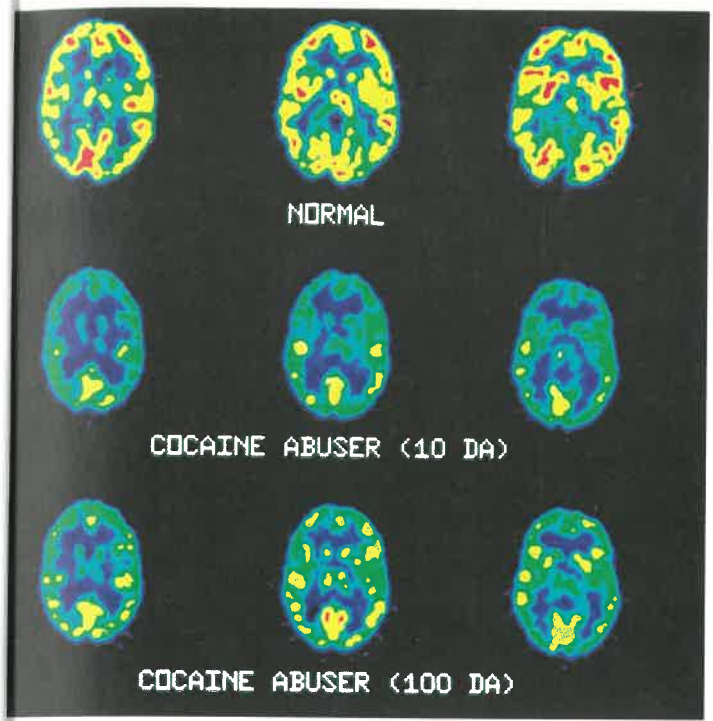
If the kind of damage that lingers in an addicted person's learning abilities also hangs on in behavioral areas, this could explain why rehabilitation programs that rely on cognitive therapy—teaching new ways to think about the need for a substance and the consequences of using it—might not be effective, 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 supports 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 a recommended duration of a 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 that unleashes a craving. And it's that phenomenon that was the purpose of my brain scans at McLean Hospital.

In my earlier years, 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 hadn't gotten high for more than a quarter-century; it was an open question how I would react to the scent of what gave me so much enjoyment back then. So after an interview with a staff psychiatrist to make sure I would be able to



PET scans show low brain activity (yellow and red) 10 days after cocaine use; at 100 days, brain is recovering.

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 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—originally used to treat tuberculosis but now known to help quiet the amygdala—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. But there are hints that a cure might not in principle be impossible. One 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." All the same, 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.

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 brain-imaging center and a professor of psychiatry 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. —ALICE PARK CONTRIBUTED TO THIS STORY □

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 14.8 million people, or 5.4% of the population, are dependent on or abuse alcohol, and 13,000 more try it for the first time every day. Alcoholics Anonymous has more than 2 million members—impressive, but only a small fraction of those who need help.

Drugs
An estimated 8.1 million people are dependent on at least one drug. On average, 27,000 try them for the first time each day. Marijuana, prescription pain relievers and prescription tranquilizers are the leading drugs of abuse. In 2018, 3.7 million people received treatment for the use of drugs and/or alcohol.

Tobacco
There are about 59 million users of tobacco products in the U.S. About 15.8% of men and 12.2% of women are cigarette smokers, with cigarette use lowest in Western states and highest in the Midwest; while youth are smoking fewer cigarettes, 21% of high school students are now vaping.

Caffeine
It's the most widely used mood-altering drug in the world and is 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 mild physical dependence. Withdrawal symptoms are experienced by about half of those trying to quit.

Food
Although food addiction is not a classifiable disorder, as many as 20% of the population may fit the criteria. Food addiction also has some overlap with binge-eating disorder (which is classified), in that it affects women much more than it does men and is linked to depression.

Gambling
Approximately 2.5 million people, or 1% of the U.S. population, have a gambling disorder, wagering heedless of the consequences. In treatment populations, about half of those with a gambling disorder have suicidal ideation, and 17% have attempted suicide.

Shopping
Research indicates that about 6% of the U.S. population are compulsive buyers, with women only slightly more likely to be affected than men. The accessibility of online shopping is thought to have fueled a worldwide surge in the wallet-draining addictive activity.

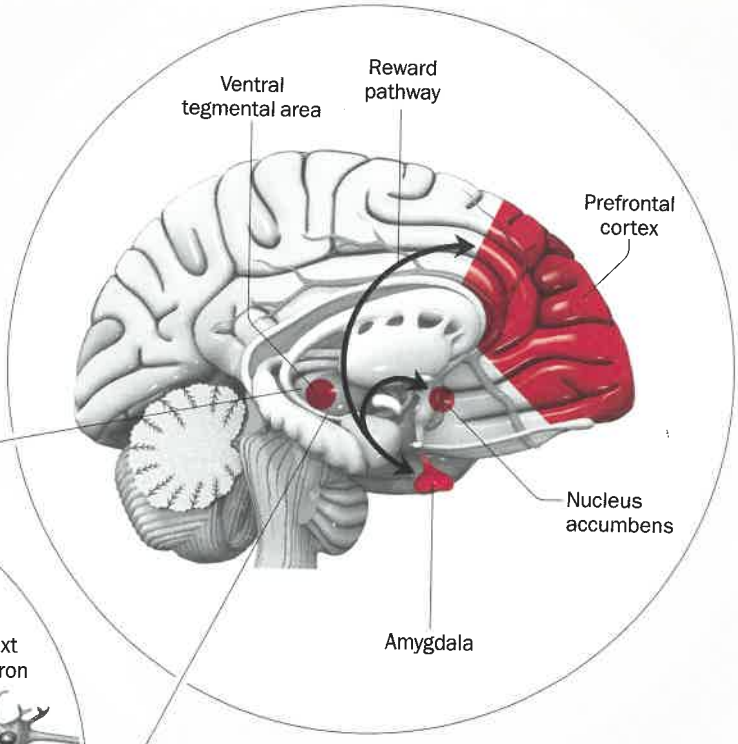
Sex
Some 3% to 6%, or 7.4 million to 14.7 million, of American adults struggle with what has recently been classified as compulsive sexual behavior disorder. Online porn addiction has escalated in recent years; excessive masturbation and other obsessive thoughts and behaviors often have a strong correlation with childhood trauma.

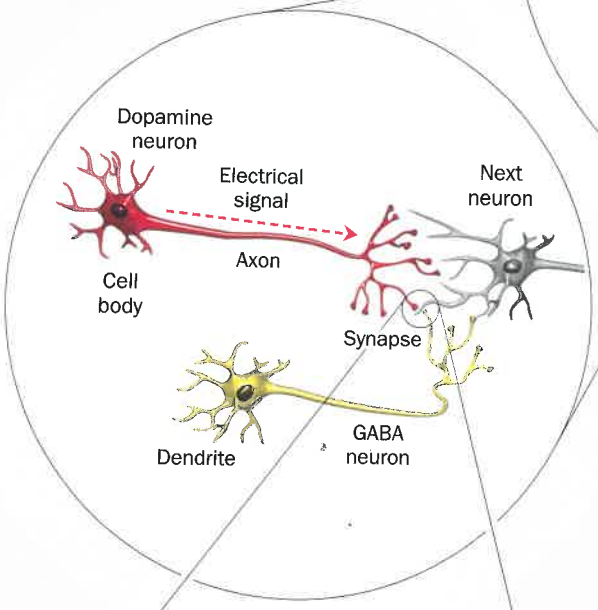
Internet
With 90% of children and teens and 65% of adults playing online and video games regularly, DSM-5 includes online gaming disorder—not as a diagnosis but a condition warranting further research. Research indicates that some heavy users develop dysfunctional symptoms that cause social, work and emotional impairment.

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.





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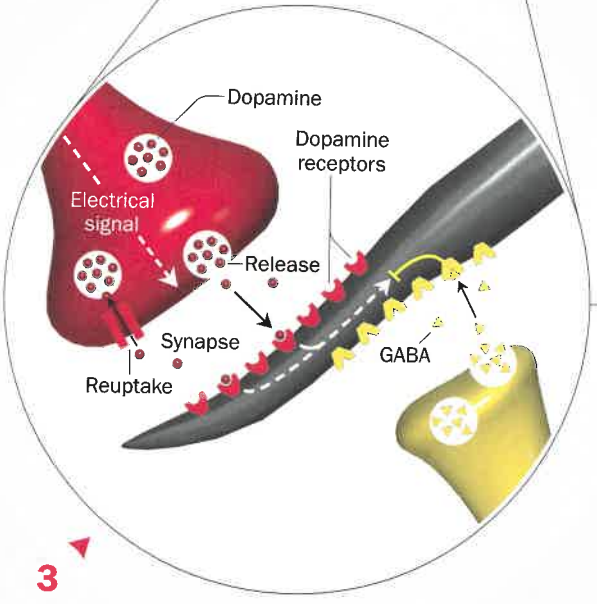
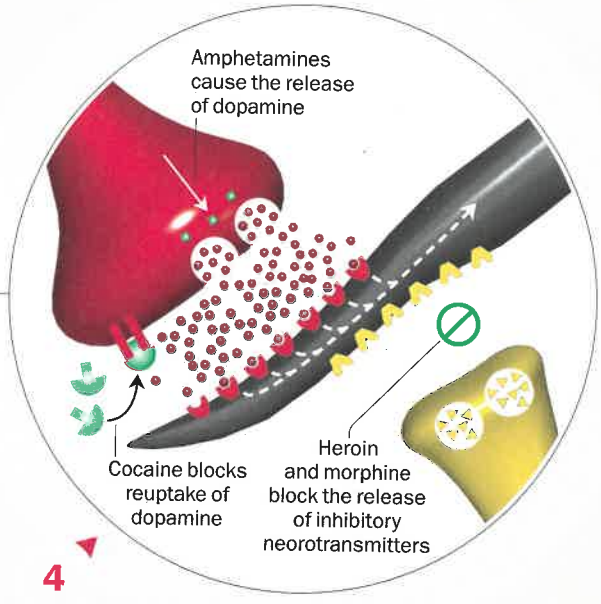
Neurons in the reward pathway communicate by sending electrical signals down their axons. The signal is passed to the next neuron across a small gap called the synapse.



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