



BEEN DOWN SO LONG IT LOOKS LIKE UP TO ME:

First dopamine whisks you into euphoria // Then compulsion displaces pleasure // Eventually, just the sight of a \$20 bill makes your brain scream cocaine // Now, is there any way to replace the brain tissue that got eaten away?

The Addicted Brain

■ BY ANITA SLOMSKI // PHOTOGRAPHS BY JAMES WORRELL

Chances are, what's inside Thomas Stanton's skull bears little resemblance to a normal brain. Stanton, a 47-year-old medical supply technician at a Veterans Administration hospital in La Jolla, Calif., has been addicted to methamphetamines for 30 years, and the damage such abuse produces tends to be severe. According to Hans Breiter, a psychiatrist who has been studying addicts for 15 years, drugs of abuse significantly remodel brain structures and circuitry, making changes that become apparent when he analyzes magnetic resonance imaging scans. Breiter, whose research will eventually examine the brains of thousands of healthy and addicted subjects, has found in early tests that cocaine addicts who also abuse alcohol have decreased brain volume and diminished cortical thickness in regions that are important for judgment and decision-making. "Preliminary data suggest that parts of their brains are not communicating with other parts," says Breiter, who directs the Phenotype Genotype Project in Addictions and Mood Disorders at the Massachusetts General Hospital.

For Stanton and other addicts, such brain alterations translate into a habit that's extremely difficult to kick. Stanton started using meth in the navy at age 17, when he needed a way to stay alert during long nights standing watch at sea. Since then, he's been in and out of prison every few years, and though he has been clean for a year and a half, an earlier attempt to quit failed after five years, when loneliness and

depression prompted a relapse. He now stays clear of former addict friends to avoid the temptation to get high. "Meth ruined my life, but there are days when I have to do everything in my power not to start again," Stanton says.

One reason drugs are so alluring, no matter the cost, is well understood. Since the 1970s, scientists have known that the chemical dopamine, unleashed in the brain by all drugs of abuse, is responsible for the euphoria that draws people into addiction. But only recently have researchers discovered more about dopamine's role—that it facilitates conditioned responses to drugs that result in compulsive abuse even when the drug itself no longer provides pleasure. When dopamine levels get out of kilter, other brain chemicals are also affected, producing profound changes in the circuitry involved with memory, inhibition, motivation and judgment. Treating addiction, scientists have found, requires much more than simply blocking the high.

Drugs of abuse alter a number of neurotransmitters—the chemicals that transmit messages across synapses from neuron to neuron—but their effect on dopamine, which influences circuits that ferry signals of pleasure, awareness, judgment and motivation, may be the most crucial one in causing addiction. Dopamine encourages behavior essential to the survival of the species. It's released when we eat, quench our thirst or have sex, making us want to repeat those activities. But taking any addictive drug also floods the

If you eat chocolate, have sex or snort cocaine and the world suddenly exceeds your expectations, you get a surge of dopamine, triggering euphoria.

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brain with dopamine, and in much greater quantities than do natural rewards such as food or sex. Animal studies have shown that eating may boost dopamine levels by as much as 50% and that sex doubles them, whereas cocaine can produce triple the normal amount, and methamphetamine causes around a tenfold increase. Moreover, the dopamine surge from addictive drugs lasts longer than a natural high.

This effect begins at the base of the brain, in the ventral tegmental area, from which neurons send their long fibers

into the nucleus accumbens, located in the midbrain, and into the frontal cortex. Dopamine attaches to cell receptors in the nucleus accumbens, initiating a cascade of biochemical events inside those neurons, which then pass the signal along to neurons in other brain regions. Normally dopamine is recycled back into the neuron that released it after transmitting its signal to the next neuron. But drugs of abuse disrupt that sequence, either releasing too much dopamine or interfering with its recycling. The chemical pools in the synapses and overwhelms the neurons, producing euphoria.

Because the brain can tolerate only so much dopamine, it may respond to repeated use of cocaine, for example, by reducing the number of a type of dopamine receptor called D2 in the nucleus accumbens. Many addicts have a marked decrease in D2 receptors, although it's not clear whether they were born with fewer, whether drug use initiated a falloff, or both.

People who are addicted to drugs and have disrupted dopamine systems, including reduced D2 receptors, get fewer rewards from food and sex—for example, the brains of cocaine abusers are stirred by erotica to a much smaller degree than are the brains of healthy subjects—and so the dopamine rush from drugs often becomes the primary source of pleasure. And if repeated drug use further diminishes dopamine receptors, addicts need ever-increasing amounts of a drug to get high.

If dopamine could be prevented from binding with receptors in the brain, one might suppose that addicts would not get a rush from drugs and would stop taking them. Yet as intuitive as that approach to therapy may seem—and it has intrigued researchers for more than 20 years—it hasn't panned out. “The rat models all look great, and we've tried an impressive list of 50 or so drugs, including such dopamine antagonists as the haloperidol that schizophrenics take, but they don't work for drug abuse,” says Elliot Stein, chief of the Neuroimaging Research Branch of the Intramural Research Program at the National Institute on Drug Abuse (NIDA) in Bethesda, Md.

That, Stein says, is because trying to block dopamine in an addict's brain is akin to closing the barn door after the horse has bolted. Drug-induced dopamine surges have already caused



a maladaptive form of learning and memory that initiates powerful cravings whenever a cue—the sight of drug paraphernalia, the friends an addict gets high with, a place of drug use or even a mood—triggers a drug association.

Normally, when there is a mismatch between reality and expectation, neurons fire, releasing dopamine. If you eat chocolate, have sex or take a drug and the world suddenly exceeds your expectations, you get a surge of dopamine. You learn to associate that surge not only with food, sex or drugs but also with other aspects of that experience. “Because drugs enhance this very powerful learning process, a drug user over-learns a response to the stimulus, so the mere sight of his drug buddy makes his brain scream cocaine,” says Stein.

But even with the horse out of the barn, as Stein puts it, it may be possible to help addicts unlearn responses to drug cues. The idea, says Nora Volkow, director of NIDA and the first researcher to conduct dopamine studies using positron-emission tomography scans, is to help an addict learn that items she associates with taking the drug—a \$20 bill, say, which can be rolled up to snort cocaine—are no longer linked with the high she got when she was taking the drug. That, in turn, might curb the release of dopamine, beginning a new cycle of learning.

Because regulating the release and recycling of dopamine has proved so difficult, many researchers have shifted their target from learning circuitry to another circuit in the cortex that drives motivational behavior (the pathways are connected, but it is not known exactly how). That circuit is governed by two neurotransmitters, glutamate and gamma-aminobutyric acid (GABA), which both play major roles in modulating the intensity of dopamine response to drugs and other stimuli.

Glutamate-producing neurons in the prefrontal cortex descend into the nucleus accumbens, where the release of glutamate may excite either dopamine cells or GABA cells, which inhibit neurons from firing. Drugs of abuse confuse these pathways, thus leading to compulsive drug-seeking and the lack of inhibitory control that contribute to an addict’s relapse.

“Dopamine is very much involved in how this circuit learns and adapts, but once the infrastructure of the circuit gets changed through drug use, it’s really GABA and glutamate that drive drug-seeking behavior,” says Peter Kalivas, professor and chair of the department of neurosciences at the Medical University of South Carolina at Charleston.

Trying to Quit for Decades

1784

SURGEON BENJAMIN RUSH

articulates the concept of alcoholism as a disease in a pamphlet, “An Inquiry into the Effects of Ardent Spirits upon the Human Body and Mind.”

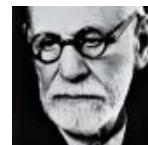
Rush’s remedy: “Taste not, handle not, touch not.”



1826

THE AMERICAN TEMPERANCE

Society is founded in Boston. Within 10 years, 1.5 million people pledge to abstain from alcohol.



1884

FREUD BEGINS PRESCRIBING

injections of cocaine, which he describes as a “magical drug,” to patients suffering from pain and depression.



1929

AMERICAN PHYSICIANS

Arthur Light and Edward Torrance try, and fail, to identify physiological reasons for the withdrawal pains morphine addicts experience.

1935

AKRON SURGEON BOB SMITH

and New York stockbroker Bill Wilson, both alcoholics, found Alcoholics Anonymous in Akron, Ohio.



1947

METHADONE IS INTRODUCED

to the United States as an analgesic, but doctors quickly tap into its potential as a treatment for heroin addiction.



1979

THE NUMBER OF ILLICIT

U.S. drug users peaks at 25 million, according to the National Household Survey on Drug Abuse.

2006

THE FDA APPROVES AN

anti-addiction drug for smokers, Chantix (varenicline). The pill partially stimulates nicotine receptors to ease withdrawal symptoms.

2006

RESEARCHERS AT

King’s College in London find that people with a specific genetic variation in their dopamine transporters are 50% more likely to become cocaine addicts.

That's why, instead of targeting dopamine, some researchers are testing what happens when GABA transmission is enhanced with anticonvulsants or muscle relaxants, or the production of glutamate is inhibited. The trick is to get a therapeutic effect without causing lethargy, cognitive slowing or loss of motivation. Kalivas is encouraged by the results of

The Unlikeliest Addicts //

Mark Stacy, associate professor of neurology at Duke University Medical Center, figured more than coincidence was at play when, during the course of two weeks in 1999, he discovered that two of his Parkinson's patients had each lost \$60,000 gambling after he increased their medication.

Then Joseph Friedman, clinical professor of neurology at Brown Medical School, reported the first case of punding—slang for the obsessive, repetitive behaviors methamphetamine addicts exhibit—in a Parkinson's patient. "He was an accountant and tallied figures over and over again," says Friedman. "Another patient couldn't stop trimming her hedges in winter, another obsessively pulled weeds and one couldn't go grocery shopping because she couldn't stop reading labels on cans." Two of Friedman's patients, both quadriplegic, became addicted to levodopa, a drug that replenishes dopamine in neurons that are failing to make enough. "They received no motor benefit from L-dopa, but they craved it like a drug addict."

Compulsive behaviors—gambling, shopping and hypersexuality are the most common—are striking in people who would be expected to have what some describe as a "Parkinson's personality," characterized by risk-averse, straitlaced behavior due to a gradual loss in dopamine production. Though it's not clear precisely what's happening, the leading hypothesis is that Parkinson's drugs that stimulate dopamine receptors in the motor-system pathway are spilling into the pathway that activates reward and motivation. Reducing the medication alleviates the behavior but may cause significant motor difficulty.

Although impulse-control disorders affect a small number of Parkinson's patients—Stacy has treated 5,000 patients and has seen only about 30 with the problem—it may provide one more clue to treating addiction. "Understanding how changing a medicine dose causes some Parkinson's patients to exhibit these destructive behaviors could help us figure out how to block that change, which may lead to treatments for addiction," says Stacy, who hopes to get funding to do fMRI studies of pathological gamblers and Parkinson's patients. —A.S.

experiments with rats and a promising Phase I human study with cocaine addicts in which an antioxidant compound, N-acetylcysteine, inhibited cravings for cocaine and dampened activity in addicts' prefrontal cortices—home to glutamate and GABA activity—when the addicts were shown drug cues. "Our guess is that this won't be a cure but that it will help restore some cognitive function," says Kalivas, "though it may not help the hard-core addict who is extremely cognitively impaired."

Yet another approach may be to amplify the dopamine response to non-drug-related stimuli, assuming researchers can find the right dopamine receptors to target. "If you can increase drug abusers' sensitivity to natural reinforcers like sex and food, then they have alternative behaviors to help them feel good," says Volkow.

Even as they crave the rush of their next hit, some addicts realize there's a cost to getting high. That's the executive brain talking—specifically, the anterior cingulate. But the executive brain, associated with decision-making and judgment, gradually loses sway as addiction takes hold. "The end stage of drug abuse is the disconnection—functionally or even structurally—of the primitive limbic brain from the more developed frontal cortical brain," explains psychiatrist and neurologist Walter Ling, director of the Integrated Substance Abuse Programs at the University of California at Los Angeles.

To test the breakdown of the brain's executive function, NIDA's Stein compared brain images of cocaine addicts with those of a control group as the subjects pressed a button to identify patterns in a rapidly changing sequence of letters. When a subject made a mistake, the anterior cingulate, which monitors and recognizes errors, did not light up on the scan nearly as brightly among cocaine users as it did among members of the control group. "The ability of the cocaine addict's brain to recognize an error was severely impeded," says Stein. "Just saying no to drugs clearly doesn't work for addicts because their brains are significantly impaired in coping with the conflict that arises when the no signal meets the yes signal brought on by a drug cue."



To be ultimately effective, addiction treatment must prevent relapse, so identifying those at high risk for relapse is vital, says Martin P. Paulus, associate chief of psychiatry at the San Diego Veterans Administration Hospital and professor of psychiatry at the University of California at San Diego. He uses brain images of methamphetamine abusers shortly after they have stopped using the drug to predict those likely to fall off the wagon. “If we have an objective measure of brain function that indicates probability of relapse,” says Paulus, “then we can appropriate resources to those who most need them.” In Paulus’s study, slightly lower levels of activity in the prefrontal cortex during decision-making tasks predicted with considerable accuracy those addicts who would relapse during the first two years after treatment.

Whether the brains of addicts can ever return to normal is an open question. “It seems to be highly variable,” says Volkow of NIDA, who has been following methamphetamine and cocaine addicts after sobriety. “Some brains recover, while others don’t. It probably depends on how long

someone has been taking the drug, how frequently and the age at which he or she began. The earlier you start, the greater the likelihood the brain changes will be longer lasting.” ■

But when the addicts were high on cocaine during this experiment, the rush of dopamine allowed their usually sluggish cingulates to approach normal levels. That suggests that a drug that increases dopamine might enhance compromised dopamine levels in the anterior cingulate and other areas and perhaps restore some of the dysfunctional dopamine circuitry. Stein also thinks that the brain’s cognitive circuitry can be bolstered by the rehabilitation of the anterior cingulate in the same way that therapy helps stroke victims relearn how to speak and move. “If we think of the anterior cingulate as a muscle that has atrophied, maybe we can use biofeedback to give people information about their cingulate activity and ask them to try to increase it, much as we might give feedback on muscle performance,” says Stein, who is writing a protocol for a clinical trial to test his idea.

→ DOSSIER

1. “Drug Addiction: The Neurobiology of Behaviour Gone Awry,” by Nora D. Volkow and Ting-Kai Li, *Nature Reviews/Neuroscience*, December 2004. Excellent overview of how addiction occurs, its neurobiology, current and potential pharmacological and cognitive-behavioral interventions, and society’s response to drug abuse.
2. “The Addicted Brain: Overview/The Evolution of Addiction,” by Eric J. Nestler and Robert C. Malenka, *Scientific American*, Feb. 9, 2004. Pioneering investigators of the molecular basis of drug addiction clearly describe the changes in the brain’s chemistry and architecture as an individual progresses from drug experimentation to intractable addiction.