ADDICTION
▶ LONG-TERM CHANGES

Beyond the Pleasure Principle

Sure, drugs feel good—but they're addicting because they co-opt memory and motivation systems, not just pleasure pathways

When it comes to kicking a drug habit, going through withdrawal is the easy part. The cold-turkey alcoholic shaking with delirium tremens might not agree, but only after the body detoxifies does the real challenge begin: staying clean. Ex-addicts with the strongest resolve—and plenty of external motivation in the form of frayed relationships, probationary jobs, or incipient lung cancer—struggle to resist cravings and are susceptible to relapse even years after their last dose.

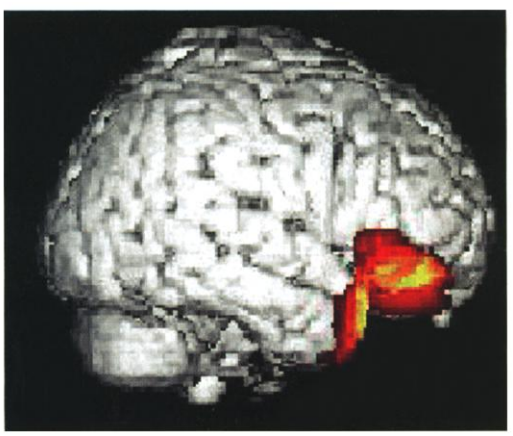
Researchers have spent decades studying the immediate effects of drugs on the brain. Drugs cause short-term surges in dopamine and other brain messengers that signal pleasure or reward. But the brain quickly adapts to this deluge; pleasure circuits overwhelmed by drugs' signals desensitize—so much so that the brain can suffer withdrawal once the binge is over.

In the past decade or so, many researchers have started to focus on a more daunting problem: the long-term consequences of drug abuse. Many drugs don't induce much pleasure after prolonged use, in part because of desensitization, or tolerance. So why do addicts keep taking their drug of choice, even when they try to abstain? To find out, researchers are seeking clues in parts of the brain that help control motivation, looking for changes that happen after weeks, months, and years of exposure to drugs.

Some of the neural changes they've found look very familiar: Addiction seems to rely on some of the same neurobiological mechanisms that underlie learning and memory, and cravings are triggered by memories and situations associated with drug use. Recent studies have revealed a "convergence between changes caused by drugs of addiction in reward circuits and changes in other brain regions mediating memory," says neuroscientist Eric Nestler of the University of Texas Southwestern Medical Center in Dallas. For instance, both learning and drug exposure resculpt synapses, initiate cascades of molecular signals that turn on genes, and change behavior in persistent ways. Understanding these processes could help addicts conquer relapse, "the core clinical problem" of addiction, says Steven Hyman, director of the National Institute of Mental Health in Bethesda, Maryland (soon to depart for Harvard University; see p. 970). "If we want to focus on the clinical issue that matters, we have to understand how associative memories are laid down that change the emotional value of drugs and create deeply ingrained behavioral responses to those cues [that trigger relapse]."

Memories you remember

Memory researchers divide memories into those you consciously remember and those you generally don't. Consciously, people may remember a past drug-induced burst of euphoria and seek out the drug again, or they may remember that drugs stop them from feeling crummy. This type of memory is "good at explaining why people take drugs, but it doesn't explain addiction," says Terry Robinson of the University of Michigan, Ann Arbor. Plenty of people dabble in drug use for just such pleasure-related reasons, but addiction is different. Once addicted, people compulsively seek out and take drugs, even if they don't provide pleasure anymore and despite a strong will to quit—a defining feature of addiction that ties it to other compulsive behaviors (see p. 980).



The face of craving. Videos containing drug-related cues stimulate the orbitofrontal cortex and temporal lobe (above) as well as deeper reward-related brain structures in addicts.

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Nonconscious memories are much more insidious, Robinson points out, and are more likely to underlie the compulsive aspect of addiction and the cravings that lead to relapse. For instance, the paraphernalia of drug use—crack pipes, syringes, the sound of ice tinkling in a glass full of scotch—can act as cues that induce craving much like the sound of a bell caused Pavlov's dogs to salivate. Even though addicts can become conscious of the relationship between some drug-related cues and their cravings, other cues might be less obvious; for instance, they might not recognize that a certain place or smell wakens a hunger for the drug. Cues "can goad an individual to drug seeking in the absence of conscious awareness," says Robinson.

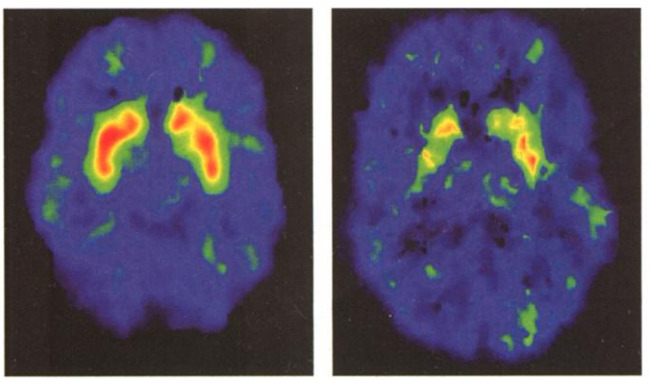
When former addicts see videos evocative of drug use, they report craving and show signs of stress, such as increased heart rate, says psychiatrist Charles O'Brien of the University of Pennsylvania in Philadelphia. Positron emission tomography (PET) shows that parts of the reward system are unusually active when people experience craving. Other researchers, particularly psychiatrist Nora Volkow of Brookhaven National Laboratory in Upton, New York, also see hyperactivation of the orbitofrontal cortex when recovered addicts see cues that induce craving for cocaine. This part of the brain is closely connected to reward pathways and is disrupted in people with obsessive-compulsive disorder. Volkow suggests that the orbitofrontal cortex is responsible for the craving and compulsion that make addicts so susceptible to relapse.

Another type of nonconscious memory, called sensitization, is less intuitive: If an animal receives a big dose of a drug—say, amphetamine, morphine, or cocaine—for several days in a row, each successive dose causes a stronger response. Behaviorally, the rat bobs its head and runs around the cage more, and inside the brain, more dopamine is released even though the drug dose is the same. The effect lasts a long time, says Robinson. His group sensitized rats to amphetamine, waited 1 year, and then gave the animals another dose. Even then, they responded more strongly than did animals without previous drug experience. Sensitization "alters neural circuitry involved in normal processes of incentive, motivation, and reward," says Robinson. This neural circuitry isn't a simple hard-wired response to the drug, however: It depends on context. If Robinson's team gives a sensitized rat another dose of the drug in a different cage from the one where it received the training doses, the animal responds normally, as if it had never experienced the drug before. Sensitization, in an environment where an animal and presumably a person has learned to expect a drug, "renders brain circuitry hypersensitive to drugs and drug-associated paraphernalia," says Robinson.

Technicolor short-circuits

Although each drug of abuse has its idiosyncratic effects, all specialize in bombarding the brain's dopamine-mediated reward cir-

cuits. Long-term abuse can wear out these pathways, reducing the number of receptors that respond to dopamine. Some of Volkow's more chilling PET scan images show the brains of former methamphetamine users: Some have been drug free for months but their dopamine systems are still not firing on all cylinders. Dopamine fuels motivation and pleasure, but it's also crucial for learning and movement. Volkow reported in the March issue of the *American Journal of Psychiatry* that the loss of dopamine transporters, a measure of how disrupted the dopamine system is, correlates with memory problems and lack of motor coordination.



Blown out. Even 80 days after detox, a methamphetamine abuser's dopamine system (right) hasn't recovered to normal levels (left).

Once the brain becomes less sensitive to dopamine, it "becomes less sensitive to natural reinforcers," Volkow says, such as the "pleasure of seeing a friend, watching a movie, the curiosity that drives exploration." The only stimuli still strong enough to activate the sputtering motivation circuit, she says, are drugs.

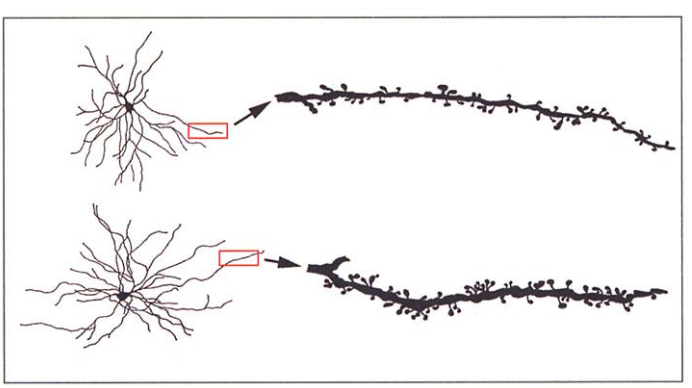
Understanding that drugs "rearrange someone's motivational priorities" can help explain some of the senseless behaviors addicts engage in, such as neglecting their families, jobs, and health, says Alan Leshner, director of the National Institute on Drug Abuse in Bethesda, Maryland. As Leshner explains, "it isn't the case that the crack-addicted mother does not love her children. She just loves drugs more."

Microscopic memories

Many recovered drug users say they fight cravings for the rest of their lives. Addiction researchers aren't sure how drugs change the brain in ways that can last a lifetime, but they aren't alone. As Nestler points out, "our field [of addiction research] and the learning and memory field have not made a lot of progress … in identifying molecular changes underlying long-term changes in memory."

They have some hunches, though, and some reasonable evidence for mechanisms that might pitch in to construct long-lasting memories or compulsions. Research on the sea snail *Aplysia* and the mouse hippocampus has uncovered a range of cellular signals that accompany learning; some of the same players are active in addiction. For example, the transcription factor CREB is necessary for learning in mice and *Drosophila*, and CREB is also boosted by drug use, suggesting that it contributes somehow to drug-mediated neural changes.

One of the best studied models of memory at the cellular level is called long-term potentiation (LTP). Memories are stored in the brain, researchers suggest, in part by changes in how neurons are interconnected. In LTP, hyperstimulation makes synapses, those points of near-contact where neurons communicate, more responsive to future stimulation—that is, it changes the connection between the two cells. In the 31 May issue of *Nature*, Mark Ungless of the University of California, San Francisco, and colleagues showed that a single dose of cocaine induced LTP in dopamine cells in a part of the brain called the ventral tegmental area that is critical for addiction (see figure on p. 982), suggesting that the same cellular mechanisms—albeit in different parts of the brain—are at work in memory and addiction.



Memento cocaine. After drug exposure, some neurons have more dendrites and connective spines (bottom) than in untreated animals (top).

Other changes in synaptic connections are more concrete: Memory researchers have found that a neuron's dendrites build more branching projections and have more synapses that connect to neurons with which the cell communicates regularly. Robinson and colleagues have found that drugs produce the same effect. When they sensitize animals to a drug, they see more dendritic branches and a greater density of neurons in the nucleus accumbens and the prefrontal cortex. Both areas are key players in processing reward signals and making decisions. These morphological changes last at least a month, Robinson says, and probably longer. Addiction researchers and memory researchers suspect that such physical changes in neurons and their connections are crucial for understanding both fields. "To me, that is the core," says Hyman. "There is no more important question in the field of addiction than understanding the mechanisms that produce and maintain altered patterns of synaptic connections."

Nestler says the basic molecular processes constructing these changes are probably the same in learning and memory and in addiction. After all, he says, "the brain is conservative" and probably has a "finite repertoire of molecular changes that it can mount in response to environmental perturbations." Nestler and his colleagues have found at least one molecule that appears to be specific for addiction, however. The protein, called Δ-FosB, builds up in the reward pathway after repeated exposure to drugs and sticks around longer than other proteins—for as long as 4 to 6 weeks after the last dose. The protein increases an animal's sensitivity to drugs and can also induce relapse if injected.

In some cases, the line between memory systems and addiction is hard to draw. For instance, Stanislav Vorel of Albert Einstein College of Medicine in New York City and colleagues reported in the 11 May issue of *Science* (p. 1175) that stimulating the hippocampus—the archetypal seat of memory in the brain—makes formerly exposed but now drug-free rats seek out cocaine. And other researchers have discovered that in some cases, dopamine in so-called pleasure circuits appears to be more important for learning—or what different labs call prediction or anticipation—than reward.

At the top of many addiction researchers' "to-do lists" is to detangle all the threads of learning and memory, motivation, and reward that make addiction addiction: Find the switch. As Leshner puts it, "we know a tremendous amount about the differences between the addicted and nonaddicted brain, both behaviorally and biologically. We know less about the transition process between the two." The processes involved in learning and memory may eventually be the key to figuring out how an often pleasurable experience—taking a drug—can change from a somewhat self-destructive hobby to a life-threatening compulsion.

–LAURA HELMUTH

CREDITS: (TOP TO BOTTOM) N. VOLKOW *ET AL.*, *AM. J. PSYCHIATRY* 158(3), 377 (2001); T. ROBINSON AND B. KOLB, *EUR. J. NEUROSCI.* 11, 1598 (1999)