

A LIFELINE FOR ADDICTS

Restoring the brain's flexibility may help addicts act on their desire to quit

BY MICHELE SOLIS

Reid had been drinking hard since 1994, when sickness, his father's death and business troubles had him reaching for more alcohol than usual. Eventually he was knocking back 10 or more drinks a day. In 2009 his family leveled an ultimatum. He had to give up alcohol or get out.

"That choice sounds real simple, but it's very, very hard," says the 58-year-old college-educated businessman, whose last name has been withheld. "I've got a wife to die for and two of the greatest kids in the world, and I'm sitting there looking in the mirror, asking myself, 'You're going to give all this up for that drink?'" he remembers. Still, he drank, secretly downing miniature bottles of vodka while walking the dog, hiding out in the bathroom or going through the car wash.

An alcoholic's sense of being trapped in old habits reflects an underlying resistance to learning that scientists are now documenting at the molecular level. Over the past five years researchers have turned up evidence that using drugs and alcohol causes a loss of flexibility in the brain, including in the regions needed for changing habits. Even brief periods of drug use damage the junctions between neurons, known as synapses. Their healthy operation is critical to translating will into action. The very structures needed to dig a person out of addiction are eroded by drug use.

Researchers are now looking for ways to replenish this flexibility with compounds that adjust how the neurotransmitter glutamate, a chemical messenger in the brain, operates at the synapses. "We're trying to restore the brain machinery that al-

lows a person to regain more control over their behavior," says Peter W. Kalivas, a professor at the Medical University of South Carolina, who studies the role of glutamate in addiction.

Returning the brain to a state where it is open to change, rather than resistant to it, could kick-start recovery. "This is not going to cure addiction, but it's definitely going to help," says Nora D. Volkow, director of the National Institute on Drug Abuse.

Drug-Induced Learning Problems

In the past scientists had focused primarily on how drugs take hold of the brain's reward regions. The new research on glutamate seeks to explain not how addiction sets in but why it is so hard to beat.

Even when addicts desperately want to stop, for fear of losing a job, a spouse or their life, they often still persist in taking drugs. Experts suspect this disconnect happens because drug use impairs a person's capacity to learn. Although scientists have long known that drug use induces a variety of cognitive shortcomings, during the past 10 years the learning deficit has emerged as a key reason why addicts stay addicted. In particular, addicts struggle to break old habits—even those not related to drug use.

This difficulty with developing a new routine can be measured in laboratory tests of "reversal learning" that ask a person to change how he or she responds to a familiar prompt. Addicts can learn an initial rule perfectly well, but they run into trouble when the rules change. In a 2006 study, for example,

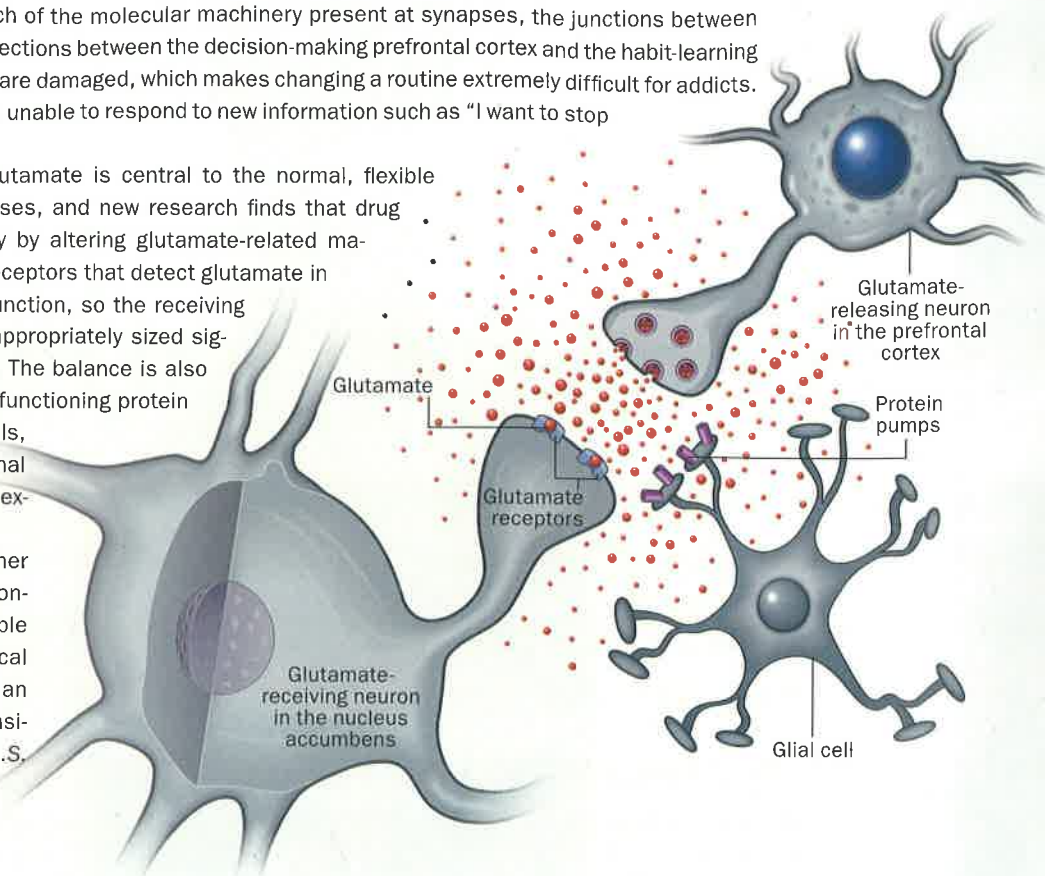


Rigid Synapses

Addiction affects much of the molecular machinery present at synapses, the junctions between brain cells. The connections between the decision-making prefrontal cortex and the habit-learning nucleus accumbens are damaged, which makes changing a routine extremely difficult for addicts. The synapses become rigid, unable to respond to new information such as “I want to stop using drugs.”

The neurotransmitter glutamate is central to the normal, flexible functioning of these synapses, and new research finds that drug use destroys that flexibility by altering glutamate-related machinery. For example, the receptors that detect glutamate in the synapse begin to malfunction, so the receiving neuron does not send an appropriately sized signal to the next cells in line. The balance is also thrown out of whack by malfunctioning protein pumps in nearby glial cells, which fail to keep up normal levels of glutamate in the extracellular space.

These problems and other types of synaptic malfunctioning seem to be correctable with common pharmaceutical drugs, which could make an addict’s decision to quit easier to implement. —M.S.



cocaine and alcohol abusers were asked to press a key each time they saw a green rectangle on a screen. After 500 repetitions, the rules changed so that the green rectangle signaled they were *not* to press the key. Healthy control participants soon withheld their key presses, but the addicts kept on pressing. Even when given feedback about their mistaken key pressing in a fol-

low-up study, addicts still stuck with the old responses.

Addiction itself can be viewed as impaired reversal learning, says David Jentsch, a neuroscientist at the University of California, Los Angeles. A person first learns the rule: “When I use drugs, I feel good.” Over time, as negative consequences accumulate, the rule changes to: “When I use drugs, bad things happen.” “They know the new rule, they know things are getting bad, they know the drug isn’t as positive as it once was,” Jentsch says. “But they’re unable to update their behavior.” Reid, for instance, would convince himself that he could handle just one drink, despite plentiful evidence to the contrary. “I’d think one beer won’t hurt, but next thing you know, I’d have blacked out,” he says.

Animal studies indicate that this inability to update is a result of drug use rather than, say, an inherent trait of those likely to try drugs. In 2002 Jentsch and his colleagues reported that daily injections of cocaine for two weeks impaired reversal learning in vervet monkeys. Nine days after the last injection, monkeys learned by trial and error which of three objects hid a food treat underneath it. Once they figured it out, the food was hidden underneath a different object, and the monkeys had to discover the new location. Cocaine-naive monkeys readily adapted their choices, but cocaine-treated monkeys did

FAST FACTS

How Addiction Takes Hold of the Brain

- 1 >>> Drug use impairs the brain’s flexibility, making it difficult to change habits.
- 2 >>> Neural communication is impaired by broken machinery at the synapses—the connections between brain cells.
- 3 >>> Repairing this machinery with pharmacological treatment can restore flexibility, allowing an addict’s desire to change to triumph over his or her habit.

not, continuing to select the object that had first hidden the food. Similar effects have since been found in rats and mice for cocaine, methamphetamine and alcohol.

Strung-Out Circuitry

Impairments in reversal learning reflect a brain working on automatic pilot. Behaviors ingrained as habits—whether looking in the same place for food or taking drugs—begin largely subconsciously until some surprise or consequence necessitates a change. The plan to change is then hatched in the

Drug-free monkeys readily adapted their choices when the food was hidden under a different object, but cocaine-treated monkeys did not.

brain's supervisory regions, within the prefrontal cortex, and implemented through that area's connections to regions that drive habitual behaviors, such as the nucleus accumbens, a sugar cube-size area buried underneath the cortex. "It's a self-control circuit," Jentsch says. "Think of it as where knowing meets doing."

These areas communicate by way of the synapses between neurons [see box on opposite page]. To send a message, a neuron in the prefrontal cortex releases glutamate onto the receiving end of a neuron in the nucleus accumbens. There the glutamate molecules bind to proteins on the cell called receptors, like keys fitting into locks. The receptors then trigger a discharge of electricity from the neuron in the nucleus accumbens, which releases more neurotransmitters through its synapses, and the message is passed on. Strong synapses translate this glutamate message into a big electrical signal, whereas weak synapses convey only blips.

Researchers are finding that these synapses are unusually rigid in addiction, as though the nucleus accumbens receives the messages from the prefrontal cortex but cannot heed the instructions. Normally a synapse's strength varies over time, depending on the pattern of previous messages sent through it. For example, the rapid-fire release of glutamate leads to long-lasting boosts in electrical output. Yet in animals exposed to cocaine, no matter how much glutamate is released or how quickly it floods the synapse, the receptors trigger the same amount of electrical activity. Similar disruptions in synaptic plasticity are also found in animals exposed to methamphetamine, nicotine and heroin.

Kalivas and Volkow propose that this loss of flexibility prevents addicts from fully using information coming from the prefrontal cortex to curb their drug habits. "It's not like the connections have been burned out completely," Kalivas says about the lost flexibility at these synapses. "It's more subtle than that, which gives us hope we can fix it."

Refurbishing Synapses

Armed with the knowledge that restoring these synapses to their original, malleable state might help addicts, researchers began trying to figure out exactly which parts of the synapse are broken by addiction. Although a synapse is only a tiny point of contact between two neurons, it relies on a vast array of molecular machinery responsible for releasing and detecting glutamate messages.

The latest research suggests that several of these synaptic components are damaged by addiction. For example, in 2003

Kalivas's team found that cocaine decreases the amount of glutamate floating outside the neurons in the nucleus accumbens, in the space that surrounds brain cells and their tiny synapses. The lack of this signaling chemical ultimately distorts the glutamate messages sent through synapses by the prefrontal cortex.

Cocaine appears to cause this deficiency by reducing the number of glutamate-supplying protein pumps located on nearby support cells called glia. These pumps work by importing an amino acid called cysteine from the extracellular space and exporting glutamate into that space. Kalivas and other researchers wondered if supplying more cysteine to the brain could bump up the glutamate supply. They turned to a common compound used to treat a Tylenol (acetaminophen) overdose and included as a mucus buster in some cough syrups. In 2009 Kalivas showed in rats that this compound, called N-acetylcysteine (NAC), spurred the brain's remaining glutamate pumps into overdrive and returned glutamate levels to normal, restoring plasticity to the synapses.

In 2011 Kalivas's group linked this NAC-induced flexibility to less relapse-like behavior in rats. In these experiments, rats initially learned to press a lever to receive cocaine intravenously, but they then learned to stop pressing after the lever started delivering saline instead. When given a small "reminder" dose of cocaine or a cue associated with the drug, the control rats began pressing the lever again. The rodents treated with NAC pressed the lever substantially less often than controls.

Drugs do more than interfere with glutamate pumps, however. They also change the synaptic machinery responsible for detecting glutamate—which means another possible target for

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N-acetylcysteine treatment reduced consumption in both adult pack-a-day smokers and teen marijuana users.



Restoring the brain's flexibility will not cure addiction by itself. Drug users will still need to nurture their desire to quit in positive environments such as support groups.

treatment. There are several types of glutamate receptors, each of which shapes the ensuing electrical signal in distinctive ways. These receptors interact, meaning that drug-induced changes to one receptor can affect other receptor types, causing a kind of domino effect of molecular adjustments. "I don't think there's one monolithic thing that's broken at this synapse, but rather one thing after another is somewhat shifted," says Marina Wolf, a neuroscientist at the Rosalind Franklin University of Medicine and Science.

In 2008 Wolf and her team found that prolonged access to cocaine spurred a long-lasting increase in an unusual kind of glutamate receptor in rats that matched an uptick in the rodents' drug cravings. In 2011 they reported that pharmacologically stimulating another type of glutamate receptor reversed the effect, possibly by instigating the removal of the unusual receptors.

Recovery Fast Track

Many of the drug-induced changes in glutamate signaling can be targeted with compounds that doctors already use for other ailments. Some glutamate receptor drugs are approved for treating disorders such as migraines or Parkinson's disease, and NAC is even sold in health food stores as an antioxidant.

Preliminary studies in humans suggest that taking NAC does indeed reduce drug use. Kalivas and his colleagues reported in a series of recent studies that three days of NAC treatment decreased—but did not eliminate—cocaine users' desire for the drug, and a similar treatment regimen halved craving intensity for cocaine, as reported by frequent users. Other studies have also found that NAC treatment in adult pack-a-day smokers

and teenage marijuana users reduced consumption in both groups.

Kalivas calls his results in humans "modest" compared to the strength of the rat studies, however. NAC may need more time to recondition the synapses in people, and it may work better when ongoing drug use does not interfere. To test this idea, Kalivas has begun a study in which participants will abstain from drugs while receiving NAC in the hospital for six weeks.

Even with new pharmacological remedies on the horizon, behavioral therapies that teach coping strategies to an addict still form a crucial part of treatment. "Restoring the synaptic machinery will not do anything on its own," Kalivas says. "A person has to have other input that will help guide him or her away from the drugs." Although people can and do beat addiction, usually through therapies such as 12-step programs, restoring the synapses pharmacologically may ease the way for the plans formulated in the prefrontal cortex to hold sway over behavior.

This type of treatment could speed up recovery for people such as Reid, who tried and failed several times to get sober after a humiliating arrest for driving under the influence, before he began taking a drug that blocks the metabolism of alcohol, so that if he has a drink he becomes sick. That threat, combined with counseling and a 12-step program, has helped him stay sober since January 2011. He says it is the hardest thing he has ever done, however, and his old habits continue to haunt him. A treatment that directly targets these habit-forming areas of the brain, such as NAC, might have made his recovery easier. "There will be a time today when I think a cold beer would really be nice," Reid says. "But I just have to get through it and move on." **M**

(Further Reading)

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- ◆ **A Double-Blind Randomized Controlled Trial of N-acetylcysteine in Cannabis-Dependent Adolescents.** K. M. Grant et al. In *American Journal of Psychiatry*, Vol. 169, No. 8, pages 805–812; August 2012.