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."

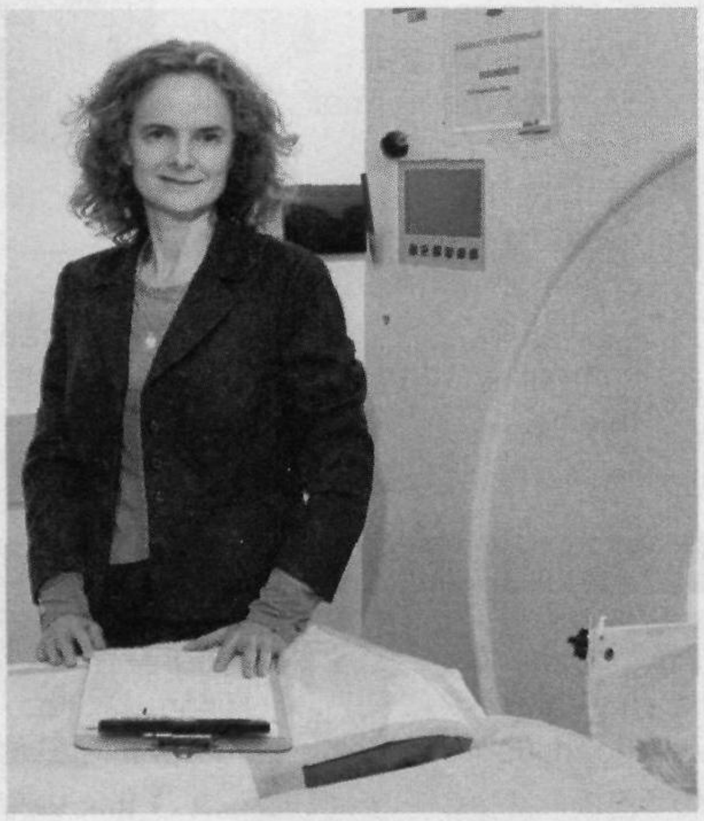
That led researchers to wonder about other biological differences in the way men

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