Harvard Medical School

Harvard Mental Health Letter

How addiction hijacks the brain

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Desire initiates the process, but learning sustains it.

The word "**addiction**" is derived from a Latin term for "**enslaved by**" or "bound to." Anyone who has struggled to overcome an addiction — or has tried to help someone else to do so — understands why.

Addiction exerts a long and powerful influence on the brain that manifests in three distinct ways: craving for the object of addiction, loss of control over its use, and continuing involvement with it despite adverse consequences. While overcoming addiction is possible, the process is often long, slow, and complicated. It took years for researchers and policymakers to arrive at this understanding.

In the 1930s, when researchers first began to investigate what caused addictive behavior, they believed that people who developed addictions were somehow morally flawed or lacking in willpower. Overcoming addiction, they thought, involved punishing miscreants or, alternately, encouraging them to muster the will to break a habit.

The scientific consensus has changed since then. Today we recognize **addiction as a chronic disease that changes both brain structure and function**. Just as cardiovascular disease damages the heart and diabetes impairs the pancreas, **addiction hijacks the brain**. Recovery from addiction involves willpower, certainly, but it is not enough to "just say no" — as the 1980s slogan suggested. Instead, people typically use multiple strategies — including psychotherapy, medication, and self-care — as they try to break the grip of an addiction.

Another shift in thinking about addiction has occurred as well. For many years, experts believed that only alcohol and powerful drugs could cause addiction. Neuroimaging technologies and more recent research, however, have shown that certain pleasurable activities, such as gambling, shopping, and sex, can also co-opt the brain. Although the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) describes multiple addictions, each tied to a specific substance or activity, consensus is emerging that these may represent multiple expressions of a common underlying brain process.

From liking to wanting

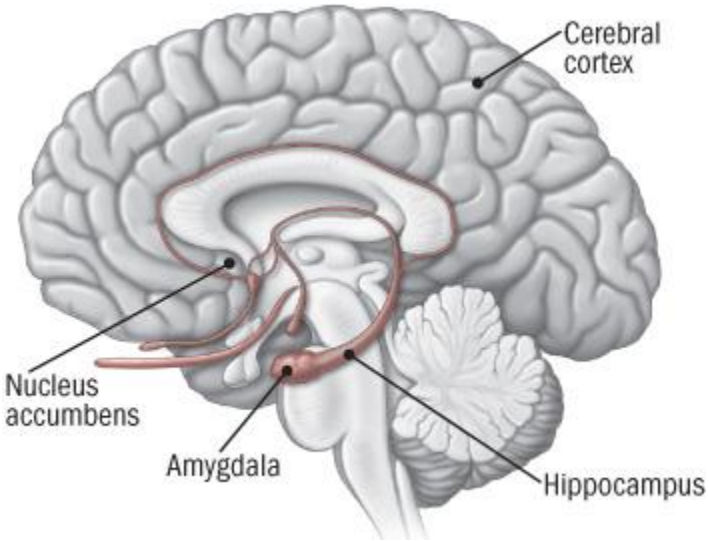
Nobody starts out intending to develop an addiction, but many people get caught in its snare. According to the latest government statistics, nearly 23 million Americans — almost one in 10 — are addicted to alcohol or other drugs. More than two-thirds of

people with addiction abuse alcohol. **The top three drugs causing addiction are marijuana**, opioid (narcotic) pain relievers, and cocaine.

Genetic vulnerability contributes to the risk of developing an addiction. Twin and adoption studies show that about 40% to 60% of susceptibility to addiction is hereditary. But behavior plays a key role, especially when it comes to reinforcing a habit.

Pleasure principle. The brain registers all pleasures in the same way, whether they originate with a psychoactive drug, a monetary reward, a sexual encounter, or a satisfying meal. In the brain, pleasure has a distinct signature: the release of the neurotransmitter dopamine in the nucleus accumbens, a cluster of nerve cells lying underneath the cerebral cortex (see illustration). Dopamine release in the nucleus accumbens is so consistently tied with pleasure that neuroscientists refer to the region as the brain's pleasure center.

The brain's reward center



Addictive drugs provide a shortcut to the brain's reward system by flooding the nucleus accumbens with dopamine. The hippocampus lays down memories of this rapid sense of satisfaction, and the amygdala creates a conditioned response to certain stimuli.

All drugs of abuse, from nicotine to heroin, cause a particularly powerful surge of dopamine in the nucleus accumbens. The likelihood that the use of a drug or participation in a rewarding activity will lead to addiction is directly linked to the speed with which it promotes dopamine release, the intensity of that release, and the reliability of that release. Even taking the same drug through different methods of administration can influence how likely it is to lead to addiction. Smoking a drug or injecting it intravenously, as opposed to swallowing it as a pill, for example, generally produces a faster, stronger dopamine signal and is more likely to lead to drug misuse.

Learning process. Scientists once believed that the experience of pleasure alone was enough to prompt people to continue seeking an addictive substance or activity. But more recent research suggests that the situation is more complicated. Dopamine not only contributes to the experience of pleasure, but also plays a role in learning and memory — two key elements in the transition from liking something to becoming addicted to it.

According to the current theory about addiction, dopamine interacts with another neurotransmitter, glutamate, to take over the brain's system of reward-related learning. This system has an important role in sustaining life because it links activities needed for human survival (such as eating and sex) with pleasure and reward. The reward circuit in the brain includes areas involved with motivation and memory as well as with pleasure. Addictive substances and behaviors stimulate the same circuit — and then overload it.

Repeated exposure to an addictive substance or behavior causes nerve cells in the nucleus accumbens and the prefrontal cortex (the area of the brain involved in planning and executing tasks) to communicate in a way that couples *liking* something with *wanting* it, in turn driving us to go after it. That is, this process motivates us to take action to seek out the source of pleasure.

Tolerance and compulsion. Over time, the brain adapts in a way that actually makes the sought-after substance or activity less pleasurable.

In nature, rewards usually come only with time and effort. Addictive drugs and behaviors provide a shortcut, flooding the brain with dopamine and other neurotransmitters. Our brains do not have an easy way to withstand the onslaught.

Addictive drugs, for example, can release two to 10 times the amount of dopamine that natural rewards do, and they do it more quickly and more reliably. In a person who becomes addicted, brain receptors become overwhelmed. The brain responds by producing less dopamine or eliminating dopamine receptors — an adaptation similar to turning the volume down on a loudspeaker when noise becomes too loud.

As a result of these adaptations, dopamine has less impact on the brain's reward center. People who develop an addiction typically find that, in time, the desired substance no longer gives them as much pleasure. They have to take more of it to obtain the same dopamine "high" because their brains have adapted — an effect known as **tolerance**.

At this point, **compulsion** takes over. The pleasure associated with an addictive drug or behavior subsides — and yet the memory of the desired effect and the need to recreate it (the *wanting*) persists. It's as though the normal machinery of motivation is no longer functioning.

The learning process mentioned earlier also comes into play. The hippocampus and the amygdala store information about environmental cues associated with the desired substance, so that it can be located again. These memories help create a conditioned

response — **intense craving** — whenever the person encounters those environmental cues.

Cravings contribute not only to addiction but to relapse after a hard-won sobriety. A person addicted to heroin may be in danger of relapse when he sees a hypodermic needle, for example, while another person might start to drink again after seeing a bottle of whiskey. Conditioned learning helps explain why people who develop an addiction risk relapse even after years of abstinence.

https://www.health.harvard.edu/newsletter_article/how-addiction-hijacks-the-brain

Resources

National Clearinghouse for Alcohol and Drug Information
P.O. Box 2345
Rockville, MD 20847
800-729-6686 (toll-free)
http://ncadi.samhsa.gov

National Institute on Alcohol Abuse and Alcoholism
5635 Fishers Lane, MSC 9304
Bethesda, MD 20892
301-443-3860
www.niaaa.nih.gov

National Institute on Drug Abuse
6001 Executive Blvd., Room 5213
Bethesda, MD 20892
301-443-1124
www.nida.nih.gov

Substance Abuse and Mental Health Services Administration
1 Choke Cherry Road
Rockville, MD 20857
877-276-4727 (toll-free)
www.samhsa.gov

The long road to recovery

Because addiction is learned and stored in the brain as memory, recovery is a slow and hesitant process in which the influence of those memories diminishes.

About 40% to 60% of people with a drug addiction experience at least one relapse after an initial recovery. While this may seem discouraging, the relapse rate is similar to that in other chronic diseases, such as high blood pressure and asthma, where 50% to 70% of people each year experience a recurrence of symptoms significant enough to require medical intervention.

Fortunately a number of effective treatments exist for addiction, usually combining self-help strategies, psychotherapy, and rehabilitation. For some types of addictions, medication may also help.

The precise plan varies based on the nature of the addiction, but all treatments are aimed at helping people to unlearn their addictions while adopting healthier coping strategies — truly a brain-based recovery program.

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For more references, please see www.health.harvard.edu/mentalextra.

Drugs, Brains, and Behavior: The Science of Addiction

Drugs and the Brain

Introducing the Human Brain

The human brain is the most complex organ in the body. This three-pound mass of gray and white matter sits at the center of all human activity—you need it to drive a car, to enjoy a meal, to breathe, to create an artistic masterpiece, and to enjoy everyday activities. The brain regulates your body's basic functions, enables you to interpret and respond to everything you experience, and shapes your behavior. In short, ***your brain is you***—everything you think and feel, and who you are.

How does the brain work?

The brain is often likened to an incredibly complex and intricate computer. Instead of electrical circuits on the silicon chips that control our electronic devices, the brain consists of billions of cells, called ***neurons***, which are organized into circuits and networks. Each neuron acts as a switch controlling the flow of information. If a neuron receives enough signals from other neurons connected to it, it "fires," sending its own signal on to other neurons in the circuit. The brain is made up of many parts with interconnected circuits that all work together as a team. Different brain circuits are responsible for coordinating and performing specific functions. Networks of neurons send signals back and forth to each other and among different parts of the brain, the spinal cord, and nerves in the rest of the body (the peripheral nervous system).

To send a message, a neuron releases a ***neurotransmitter*** into the gap (or *synapse)* between it and the next cell. The neurotransmitter crosses the synapse and attaches to receptors on the receiving neuron, like a key into a lock. This causes changes in the receiving cell. Other molecules called ***transporters*** recycle neurotransmitters (that is, bring them back into the neuron that released them), thereby limiting or shutting off the signal between neurons.

How do drugs work in the brain?

Drugs interfere with the way neurons send, receive, and process signals via neurotransmitters. Some drugs, such as **marijuana** and heroin, can activate neurons because their chemical structure mimics that of a natural neurotransmitter in the body. This allows the drugs to attach onto and activate the neurons. Although these drugs mimic the brain's own chemicals, they don't activate neurons in the same way as a natural neurotransmitter, and they lead to abnormal messages being sent through the network.

Other drugs, such as amphetamine or cocaine, can cause the neurons to release abnormally large amounts of natural neurotransmitters or prevent the normal recycling of these brain chemicals by interfering with transporters. This too amplifies or disrupts the normal communication between neurons.

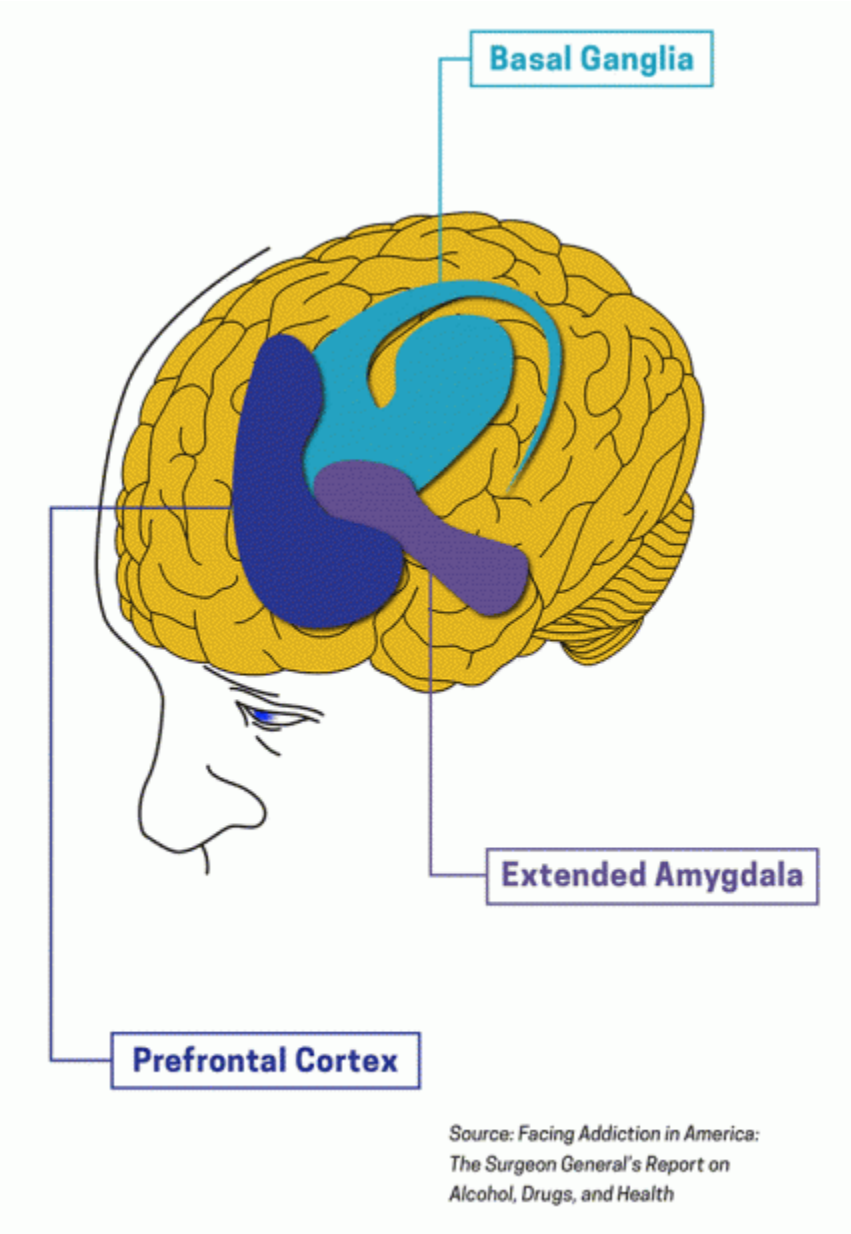
What parts of the brain are affected by drug use?

Drugs can alter important brain areas that are necessary for life-sustaining functions and can drive the compulsive drug use that marks addiction. Brain areas affected by drug use include:

- *The **basal ganglia***, which play an important role in positive forms of motivation, including the pleasurable effects of healthy activities like eating, socializing, and sex, and are also involved in the formation of habits and routines. These areas form a key node of what is sometimes called the brain's "reward circuit." Drugs over-activate this circuit, producing the euphoria of the drug high; but with repeated exposure, the circuit adapts to the presence of the drug, diminishing its sensitivity and making it hard to feel pleasure from anything besides the drug.
- *The **extended amygdala*** plays a role in stressful feelings like anxiety, irritability, and unease, which characterize withdrawal after the drug high fades and thus motivates the person to seek the drug again. This circuit becomes increasingly sensitive with increased drug use. Over time, a person with substance use disorder uses drugs to get temporary relief from this discomfort rather than to get high.

- *The **prefrontal cortex*** powers the ability to think, plan, solve problems, make decisions, and exert self-control over impulses. This is also the last part of the brain to mature, making teens most vulnerable. Shifting balance between this circuit and the reward and stress circuits of the basal ganglia and extended amygdala make a person with a substance use disorder seek the drug compulsively with reduced impulse control.

Some drugs like opioids also affect other parts of the brain, such as the brain stem, which controls basic functions critical to life, such as heart rate, breathing, and sleeping explaining why overdoses can cause depressed breathing and death.



Source: Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health

How do drugs produce pleasure?

Pleasure or euphoria—the high from drugs—is still poorly understood, but probably involves surges of chemical signaling compounds including the body's natural opioids (endorphins) and other neurotransmitters in parts of the basal ganglia (the reward circuit). When some drugs are taken, they can cause surges of these neurotransmitters much greater than the smaller bursts naturally produced in association with healthy rewards like eating, music, creative pursuits, or social interaction.

It was once thought that surges of the neurotransmitter ***dopamine*** produced by drugs directly caused the euphoria, but scientists now think dopamine has more to do with getting us to repeat pleasurable activities (reinforcement) than with producing pleasure directly.

How does dopamine reinforce drug use?

Our brains are wired to increase the odds that we will repeat pleasurable activities. The neurotransmitter dopamine is central to this. Whenever the reward circuit is activated by a healthy, pleasurable experience, a burst of dopamine signals that something important is happening that needs to be remembered. This dopamine signal causes changes in neural connectivity that make it easier to repeat the activity again and again without thinking about it, leading to the formation of habits.

Just as drugs produce intense euphoria, they also produce much larger surges of dopamine, powerfully reinforcing the connection between consumption of the drug, the resulting pleasure, and all the external cues linked to the experience. Large surges of dopamine "teach" the brain to seek drugs at the expense of other, healthier goals and activities.

Simple activities in everyday life can produce small bursts of neurotransmitters in the brain bringing pleasurable feelings. Drugs can hijack that process.

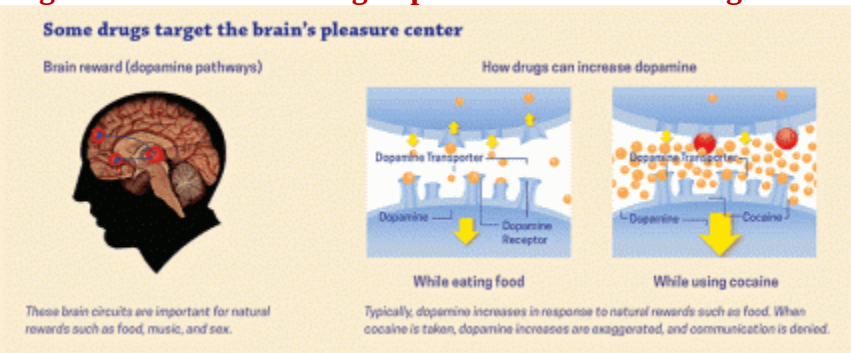
Cues in a person's daily routine or environment that have become linked with drug use because of changes to the reward circuit can trigger uncontrollable cravings whenever the person is exposed to these cues, even if the drug itself is not available. This learned "reflex" can last a long time, even in people who haven't used drugs in many years. For example, people who have been drug free for a decade can experience cravings when returning to an old neighborhood or house where they used drugs. Like riding a bike, the brain remembers.

Why are drugs more addictive than natural rewards?

For the brain, the difference between normal rewards and drug rewards can be likened to the difference between someone whispering into your ear and someone shouting into a microphone. Just as we turn down the volume on a radio that is too loud, the brain of someone who misuses **drugs** adjusts by producing fewer neurotransmitters in the reward circuit, or by **reducing** the number of receptors that can receive signals. As a result, **the person's ability to experience pleasure from naturally rewarding (i.e., reinforcing) activities is also reduced.**

This is why a person who misuses drugs eventually feels flat, without motivation, lifeless, and/or depressed, and is unable to enjoy things that were previously pleasurable. Now, the

person needs to keep taking drugs to experience even a normal level of reward—which only makes the problem worse, like a vicious cycle. Also, the person will often need to take larger amounts of the drug to produce the familiar high—an effect known as *tolerance*.



Long-term drug use impairs brain functioning.

For more information on drugs and the brain, order NIDA's Teaching Packets or the Mind Matters series at www.drugabuse.gov/parent-teacher.html. These items and others are available to the public free of charge.

https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/drugs-brain

National Institute on Drug Abuse for Teens
Advancing Addiction Science

Brain and Addiction

- DRUG FACTS

Revised December 2014

Your Brain

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Your brain is who you are. It's what allows you to think, breathe, move, speak, and feel. It's just 3 pounds of gray-and-white matter that rests in your skull, and it is your own personal "mission control." Information from your environment—both outside (like what your eyes see and skin feels) and inside (like your heart rate and body temperature)—makes its way to the brain, which receives, processes, and integrates it so that you can survive and function under all sorts of changing circumstances and learn from experience. The brain is always working, even when you're sleeping. (Learn more about the brain-body connection.)

The brain is made up of many parts that all work together as a team. Each of these different parts has a specific and important job to do.

When drugs enter the brain, they interfere with its normal processing and can eventually lead to changes in how well it works. Over time, drug use can lead to addiction, a devastating brain disease in which people can't stop using drugs even when they really

want to and even after it causes terrible consequences to their health and other parts of their lives.

See answers to common questions about drugs and use.

Drugs affect three primary areas of the brain:

- **The brain stem** is in charge of all the functions our body needs to stay alive—breathing, moving blood, and digesting food. It also links the brain with the spinal cord, which runs down the back and moves muscles and limbs as well as lets the brain know what's happening to the body.

- **The limbic system** links together a bunch of brain structures that control our emotional responses, such as feeling pleasure when we eat chocolate. The good feelings motivate us to repeat the behavior, which is good because eating is critical to our lives.

- **The cerebral cortex** is the mushroom-shaped outer part of the brain (the gray matter). In humans, it is so big that it makes up about three-fourths of the entire brain. It's divided into four areas, called lobes, which control specific functions. Some areas process information from our senses, allowing us to see, feel, hear, and taste. The front part of the cortex, known as the frontal cortex or forebrain, is the thinking center. It powers our ability to think, plan, solve problems, and make decisions.
- **How does your brain communicate?**

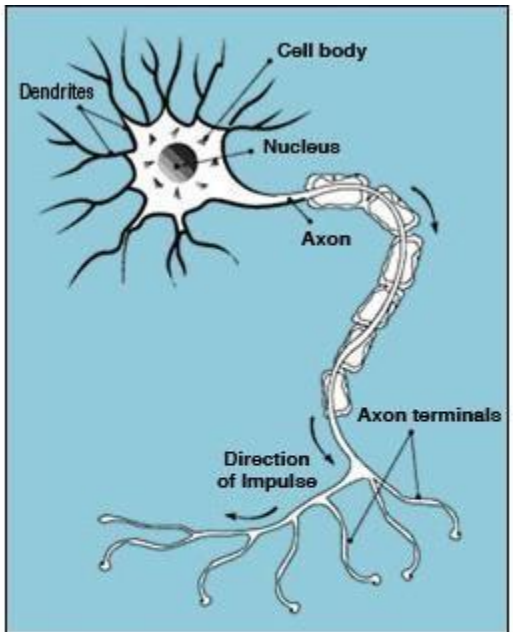


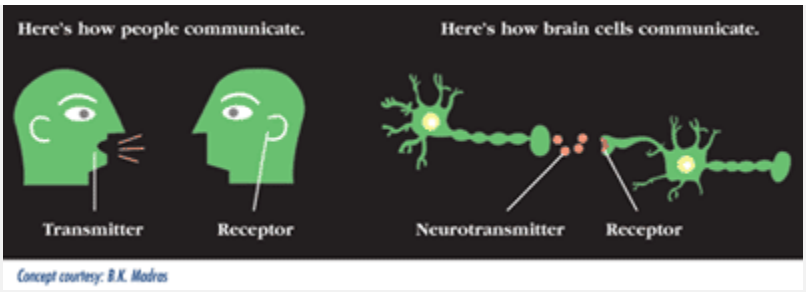
Figure 1. Neurons: Building Blocks of the Brain
The brain is made up of billions of nerve cells, also known as **neurons**. Neurons communicate with other neurons through a process known as neurotransmission.

The brain is a complex communications network of billions of neurons, or nerve cells. Networks of neurons pass messages back and forth thousands of times a minute within the brain, spinal column, and nerves. These nerve networks control everything we feel, think, and do. Understanding these networks helps in understanding how drugs affect the brain. The networks are made up of:

- **Neurons**
  Your brain contains about 100 billion neurons—nerve cells that work nonstop to send and receive messages. Within a neuron, messages travel from the cell body down the axon to the axon terminal in the form of electrical impulses. From there, the message is sent to other neurons with the help of neurotransmitters.

- **Neurotransmitters—The Brain's Chemical Messengers**
  To make messages jump from one neuron to another, the neuron creates chemical messengers, called neurotransmitters. The axon terminal releases neurotransmitters that travel across the space (called the synapse) to nearby neurons. Then the transmitter attaches to receptors on the nearby neuron.

- **Receptors—The Brain's Chemical Receivers**



To send a message, a nerve cell releases a chemical (neurotransmitter) into the space separating two nerve cells, called the synapse. The neurotransmitter crosses the synapse and attaches to proteins (receptors) on the receiving nerve cell. This causes changes in the receiving nerve cell, and the message is delivered.

As the neurotransmitter approaches the nearby neuron, it attaches to a special site on that neuron called a receptor. A neurotransmitter and its receptor operate like a key and lock, in that a very specific mechanism makes sure that each receptor will forward the right message only after interacting with the right kind of neurotransmitter.

- **Transporters—The Brain's Chemical Recyclers**
  Once neurotransmitters do their job, they are pulled back into their original neuron by transporters. This recycling process shuts off the signal between the neurons.

- ## How do drugs affect your brain?

Drugs are chemicals. When someone puts these chemicals into their body, either by smoking, injecting, inhaling, or eating them, they tap into the brain's communication system and tamper with the way nerve cells normally send, receive, and process information. Different drugs—because of their chemical structures—work differently. We know there are at least two ways drugs work in the brain:

- Imitating the brain's natural chemical messengers
- Overstimulating the "reward circuit" of the brain

Some drugs, like **marijuana** and heroin, have chemical structures that mimic that of a neurotransmitter that naturally occurs in our bodies. In fact, these drugs can "fool" our receptors, lock onto them, and activate the nerve cells. However, they don't work the same way as a natural neurotransmitter, and the neurons wind up sending abnormal messages through the brain, which can cause problems both for our brains as well as our bodies.

Other drugs, such as cocaine and methamphetamine, cause nerve cells to release too much dopamine, which is a natural neurotransmitter, or prevent the normal recycling of dopamine. This leads to exaggerated messages in the brain, causing problems with communication channels. It's like the difference between someone whispering in your ear versus someone shouting in a microphone.

The "High" From Drugs/Pleasure Effect

Scientists used to assume that the rush of dopamine alone caused the feeling of euphoria (happiness) during drug use, but they now know it is more complicated than that. Most drugs of abuse—nicotine, cocaine, **marijuana**, and others—affect the brain's "reward" circuit, which is part of the limbic system. Normally, the reward circuit responds to healthy, pleasurable activities by releasing the neurotransmitter dopamine, which teaches other parts of the brain to repeat those activities. Drugs take control of this system, releasing large amounts of dopamine—first in response to the drug but later mainly in response to other cues associated with the drug—like being with people you used drugs with, or being in places where you used drugs. The brain remembers, and the result is an intense motivation to seek and use the drug again. So dopamine does not cause the rush of feelings; instead it reinforces the desire to use drugs.

The Repeat Effect

Our brains are wired to make sure we will repeat healthy activities, like eating, by connecting those activities with feeling good. Whenever this reward circuit is kick-started, the brain notes that something important is happening that needs to be

remembered, and teaches us to do it again and again, without thinking about it. Because drugs of abuse come in and "hijack" the same circuit, people learn to use drugs in the same way.

After repeated drug use, the brain starts to adjust to the surges of dopamine. Neurons may begin to reduce the number of dopamine receptors or simply make less dopamine. The result is less dopamine signaling in the brain—like turning down the volume on the dopamine signal. Because some drugs are toxic, some neurons also may die.

As a result, the ability to feel any pleasure is reduced. The person feels flat, lifeless, and depressed, and is unable to enjoy things that once brought pleasure. Dopamine encourages the brain to repeat the pleasurable activity of drug taking. Now the person needs drugs just to feel normal, an effect known as tolerance.

Watch our video Why Are Drugs So Hard To Quit? to learn more.

Long-Term Effects

Drug use can eventually lead to dramatic changes in neurons and brain circuits. These changes can still be present even after the person has stopped taking drugs. This is more likely to happen when a drug is taken over and over.

What is drug addiction?

Addiction is a chronic brain disease that causes a person to compulsively seek out drugs, despite the harm they cause. The first time a person uses drugs, it's usually a free choice they've made. However, repeated drug use causes the brain to change which drives a person to seek out and use drugs over and over, despite negative effects such as stealing, losing friends, family problems, or other physical or mental problems brought on by drug use—this is addiction.

What factors increase the risk for addiction?

Although we know what happens to the brain when someone becomes addicted, we can't predict how many times a person must use a drug before becoming addicted. A combination of factors related to your genes, environment, and development increase the chance that taking drugs can lead to addiction:

- **Home and family.** Parents or older family members who abuse alcohol or drugs, or who are involved in criminal behavior, can increase young people's risks for developing their own drug problems.

- **Peers and school.** Friends and acquaintances who abuse drugs can sway young people to try drugs for the first time. Academic failure or poor social skills can also put a person at risk for drug use.

- **Early use.** Although taking drugs at any age can lead to addiction, research shows that the earlier a person begins to use drugs, the more likely they are to progress to more serious use. This may reflect the harmful effect that drugs can have on the developing brain. It also may be the result of early biological and social factors, such as genetics, mental illness, unstable family relationships, and exposure to physical or sexual abuse. Still, the fact remains that early use is a strong indicator of problems ahead—among them, substance abuse and addiction.

- **Method of use.** Smoking a drug or injecting it into a vein increases its addictive potential. Both smoked and injected drugs enter the brain within seconds, producing a powerful rush of pleasure. However, this intense "high" can fade within a few minutes, taking the person down to lower levels. Scientists believe that this low feeling drives individuals to repeat drug use in an attempt to recapture the high pleasurable state.

Learn more about what puts you at risk, view our video Anyone Can Become Addicted to Drugs.

Can you die if you use drugs?

Yes, deaths from drug overdose have been rising steadily over the last decade, largely due to increases in misuse of opioids. In 2017, more than 70,200 people died from a drug overdose. More than three out of five of those drug overdose deaths involved some type of opioid, either prescription pain reliever, heroin, or man-made opioids like fentanyl. The year prior, 2016, more than 63,000 people died from a drug overdose. Among young people, just over 5,400 deaths from a drug overdose occurred in 2017.[1] Young males were two times more likely to die from a drug overdose than were females.

In addition, death can occur from the long-term effects of drugs. For example, use of tobacco products can cause cancer, which may result in death. Learn more about drug overdoses in youth.

[1] Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death 1999-2017 on CDC WONDER Online Database, released 2018. Available at http://wonder.cdc.gov.

Are there effective treatments for drug addiction?

Yes, there are treatments, but there is no cure for drug addiction yet. Addiction is often a disease that is long-lasting (sometimes referred to as chronic). As with other chronic

diseases, like diabetes or heart disease, people learn to manage their condition. Scientific research has shown that 13 basic principles are the foundation for effective drug addiction treatment. Find out more in *NIDA's Principles of Drug Addiction Treatment: A Research-Based Guide* or from *Principles of Adolescent Substance Use Disorder Treatment: A Research-Based Guide.*

Types of Treatment

Treatment will vary for each person, depending on the type of drugs used and the person's specific circumstances. Generally, there are two types of treatment for drug addiction:

- **Behavior change,** in which people learn to change their behavior
- **Medications,** which can help treat addictions to some drugs, such as tobacco, alcohol, heroin, or other opioids

Length of Treatment

Like diabetes and even asthma, drug addiction typically is a long-lasting disorder. Most people who have become addicted to drugs need long term treatment and, many times, repeated treatments—much like a person who has asthma needs to constantly watch changes in medication and exercise. The important point is that even when someone relapses and begins abusing drugs again, they should not give up hope. Rather, they need to go back to treatment or change their current treatment. In fact, setbacks are likely. Even people with diabetes may go off their diet or miss an insulin injection, and their symptoms will recur—that's a cue to get back on track, not to view treatment as a failure.

Motivation for Treatment

Most people go into drug treatment either because a court ordered them to do so or because loved ones wanted them to seek treatment. The good news is that, according to scientific studies, people can benefit from treatment regardless of whether or not they chose to go into treatment.

How do I know if someone has a drug problem?

There are questions people can ask to gauge whether or not a person has a drug problem. These may not mean that someone is addicted, but answering yes to any of these questions may suggest a developing problem, which could require follow up with a professional drug treatment specialist. These include:

1. Have you ever ridden in a car driven by someone (including yourself) who had been using alcohol or drugs?
2. Do you ever use alcohol or drugs to relax, to feel better about yourself, or to fit in?
3. Do you ever use alcohol or drugs when you are alone?
4. Do you ever forget things you did while using alcohol or drugs?
5. Do family or friends ever tell you to cut down on your use of alcohol or drugs?
6. Have you ever gotten into trouble while you were using alcohol or drugs?

What should I do if someone I know needs help?

If you, or a friend, are in crisis and need to speak with someone now:

- **Call the National Suicide Prevention Lifeline at 1-800-273-TALK** (they don't just talk about suicide—they cover a lot of issues and will help put you in touch with someone close by)

If you want to help a friend, you can:

- Share resources from this site, including this page.
- Point your friend to NIDA's Step by Step Guide for Teens and Young Adults.
- Encourage your friend to speak with a trusted adult.

If a friend is using drugs, you might have to step away from the friendship for a while. It is important to protect your own mental health and not put yourself in situations where drugs are being used.

For more information on how to help a friend or loved one, visit our Have a Drug Problem, Need Help? page.

Where can I get more information?

Drug Facts

NIDA Resources:

- Mind Matters: Drugs and the Brain
- Drugs, Brains, and Behavior: The Science of Addiction
- The Brain: Understanding Neurobiology Through the Study of Addiction, Educator Curriculum
- The Brain: Understanding Neurobiology Through the Study of Addiction, Teen Activities

- **Treatment**

NIDA Resources:

- DrugFacts: Treatment Approaches for Drug Addiction
- Principals of Drug Addiction Treatment: A Research-Based Guide

Other Resources:

- Video: "Adolescent Substance Use, Addiction, and Treatment" with Sarah Bagley, M.D. [Office of Adolescent Health]

Statistics and Trends

NIDA Resources:

- DrugFacts: High School and Youth Trends

Other Resources:

- Monitoring the Future [Monitoring the Future (University of Michigan)]
- National Survey on Drug Use and Health [Substance Abuse and Mental Health Services Administration]

https://teens.drugabuse.gov/drug-facts/brain-and-addiction

National Center for Biotechnology Information
National Library of Medicine
National Institute of Health

Biology of Addiction

Drugs and Alcohol Can Hijack Your Brain

People with addiction lose control over their actions. They crave and seek out drugs, alcohol, or other substances no matter what the cost—even at the risk of damaging friendships, hurting family, or losing jobs. What is it about addiction that makes people behave in such destructive ways? And why is it so hard to quit?

NIH-funded scientists are working to learn more about the biology of addiction. They've shown that addiction is a long-lasting and complex brain disease, and that current treatments can help people control their addictions. But even for those who've successfully quit, there's always a risk of the addiction returning, which is called relapse.

The biological basis of addiction helps to explain why people need much more than good intentions or willpower to break their addictions.

"A common misperception is that addiction is a choice or moral problem, and all you have to do is stop. But nothing could be further from the truth," says Dr. George Koob, director of NIH's National Institute on Alcohol Abuse and Alcoholism. "The brain actually changes with addiction, and it takes a good deal of work to get it back to its normal state. The more drugs or alcohol you've taken, the more disruptive it is to the brain."

Researchers have found that much of addiction's power lies in its ability to hijack and even destroy key brain regions that are meant to help us survive.

A healthy brain rewards healthy behaviors—like exercising, eating, or bonding with loved ones. It does this by switching on brain circuits that make you feel wonderful, which then motivates you to repeat those behaviors. In contrast, when you're in danger, a healthy brain pushes your body to react quickly with fear or alarm, so you'll get out of harm's way. If you're tempted by something questionable—like eating ice cream before dinner or buying things you can't afford—the front regions of your brain can help you decide if the consequences are worth the actions.

But when you're becoming addicted to a substance, that normal hardwiring of helpful brain processes can begin to work against you. Drugs or alcohol can hijack the pleasure/reward circuits in your brain and hook you into wanting more and more. Addiction can also send your emotional danger-sensing circuits into overdrive, making you feel anxious and stressed when you're not using the drugs or alcohol. At this stage,

people often use drugs or alcohol to keep from feeling bad rather than for their pleasurable effects.

To add to that, repeated use of drugs can damage the essential decision-making center at the front of the brain. This area, known as the prefrontal cortex, is the very region that should help you recognize the harms of using addictive substances.

“Brain imaging studies of people addicted to drugs or alcohol show decreased activity in this frontal cortex,” says Dr. Nora Volkow, director of NIH’s National Institute on Drug Abuse. “When the frontal cortex isn’t working properly, people can’t make the decision to stop taking the drug—even if they realize the price of taking that drug may be extremely high, and they might lose custody of their children or end up in jail. Nonetheless, they take it.”

Scientists don’t yet understand why some people become addicted while others don’t. Addiction tends to run in families, and certain types of **genes** have been linked to different forms of addiction. But not all members of an affected family are necessarily prone to addiction. “As with heart disease or diabetes, there’s no one gene that makes you vulnerable,” Koob says.

Other factors can also raise your chances of addiction. “Growing up with an alcoholic; being abused as a child; being exposed to extraordinary stress—all of these social factors can contribute to the risk for alcohol addiction or drug abuse,” Koob says. “And with drugs or underage drinking, the earlier you start, the greater the likelihood of having alcohol use disorder or addiction later in life.”

Teens are especially vulnerable to possible addiction because their brains are not yet fully developed—particularly the frontal regions that help with impulse control and assessing risk. Pleasure circuits in adolescent brains also operate in overdrive, making drug and alcohol use even more rewarding and enticing.

NIH is launching a new nationwide study to learn more about how teen brains are altered by alcohol, tobacco, **marijuana**, and other drugs. Researchers will use brain scans and other tools to assess more than 10,000 youth over a 10-year span. The study will track the links between substance use and brain changes, academic achievement, IQ, thinking skills, and mental health over time.

Although there’s much still to learn, we do know that prevention is critical to reducing the harms of addiction. “Childhood and adolescence are times when parents can get involved and teach their kids about a healthy lifestyle and activities that can protect against the use of drugs,” Volkow says. “Physical activity is important, as well as getting engaged in work, science projects, art, or social networks that do not promote use of drugs.”

To treat addiction, scientists have identified several medications and behavioral therapies—especially when used in combination—that can help people stop using specific substances and prevent relapse. Unfortunately, no medications are yet available

to treat addiction to stimulants such as cocaine or methamphetamine, but behavioral therapies can help.

“Treatment depends to a large extent on the severity of addiction and the individual person,” Koob adds. “Some people can stop cigarette smoking and alcohol use disorders on their own. More severe cases might require months or even years of treatment and follow-up, with real efforts by the individual and usually complete abstinence from the substance afterward.”

NIH-funded researchers are also evaluating experimental therapies that might enhance the effectiveness of established treatments. Mindfulness meditation and magnetic stimulation of the brain are being assessed for their ability to strengthen brain circuits that have been harmed by addiction. Scientists are also examining the potential of vaccines against nicotine, cocaine, and other drugs, which might prevent the drug from entering the brain.

“Addiction is a devastating disease, with a relatively high death rate and serious social consequences,” Volkow says. “We’re exploring multiple strategies so individuals will eventually have more treatment options, which will increase their chances of success to help them stop taking the drug.”

To find publicly funded addiction treatment centers in your state, call 1-800-622-HELP, or visit https://findtreatment.samhsa.gov/(link is external).

www.ncbi.nlm.nih.gov/pubmed

How Does Addiction Physically Change the Brain?

- Posted in **Alcoholism**, **Drug Addiction**

On This Page:

By Martha McLaughlin

The human brain is a marvelously complex organ with areas that specialize in different tasks. As brain science develops, researchers are beginning to more fully understand how substance abuse and addiction affect it. These changes can be observed in many regions of the brain, including the prefrontal cortex, the nucleus accumbens and the anterior cingulate cortex (ACC).

Let's take a closer look at each of those areas below.

Drugs and Dopamine

The prefrontal cortex — involved with planning and carrying out activities — works together with the nucleus accumbens — a cluster of nerve cells located under the cerebral cortex — to turn substance use into abuse and addiction.

When people experience pleasure, the neurotransmitter dopamine is released in the nucleus accumbens. All drugs of abuse raise dopamine, and the risk of addiction is tied to the speed, intensity and reliability of the surge. Drugs may release up to 10 times more dopamine than natural rewards do.

The nucleus accumbens and the prefrontal cortex ensure that enjoying an activity is linked with wanting to repeat it. The prefrontal cortex motivates action to continue doing whatever caused the dopamine levels to rise.

Because dopamine levels produced by drugs of abuse are so much higher than what the body considers normal, it compensates in an attempt to restore balance. The body may adapt in a number of ways. It may reduce the number of dopamine receptor cells in the brain or increase the

number of dopamine transporters, which clear the neurotransmitter from the gaps between nerve cells.

These adaptations cause drug tolerance — the need to increase dosage in order to feel the effects a lower dose once produced. They also explain anhedonia, the inability to feel pleasure from normal activities, which is a common symptom in addicted individuals and those in early recovery.

Conflicts and Decisions

Another way the body responds to addiction is to shrink and weaken the ACC, the part of the brain that links pain and conflict with thoughts and behaviors. Dr. Nicole Gravagna notes that healthy brains feel pain, evaluate risks and danger, and make decisions based on the information received. By influencing the ACC, substance abuse makes it more difficult for people to handle conflict. Gravagna states that people become "conflict-stupid," and their ability to get past the pain of opposition is impaired.[1]

The ACC evaluates rewards and punishments and works with other brain regions to use that information to guide decisions. A study reported by *Science Daily* looked at the brain activity of adolescent boys with conduct and substance use disorders. They were found to have significantly less activity in the ACC and other key areas while engaged in decision-making tasks. When playing a game, they responded less than normal to wins and more than normal to losses.[2]

The effect of drugs and alcohol on the ACC can become part of a self-perpetuating cycle, where conflict and pain are felt more deeply, and people turn to substances to numb the feelings. ACC-related impairments may also make it difficult for people to clearly evaluate the risks of their substance abuse.

Age and Gender Differences

Because their brains are still developing, brain changes are often more pronounced and long-lasting in teens than in adults. The part of the brain most involved in overriding impulses and making rational decisions isn't fully developed until the mid-20s. Unfortunately, drug use can interfere with that process and slow development even further.

There are also gender differences in how addiction changes the brain. Researchers at Boston University studied individuals who had once been heavy drinkers and found that the length of time that alcohol had been abused corresponded to smaller areas of white matter. In men, the corpus callosum region of the brain was most affected, but in women the losses were seen in the cortex.[3]

Healing and Recovery

Some of the effects of drug and alcohol on the brain, such as the death of neurons, appear to be permanent. But in many ways, the brain can change itself, and a significant degree of healing is possible. Addiction-related changes in the ACC, for example, are often seen to reverse after people recover.

It's not easy to predict how long it will take the brain to heal. Some changes occur quickly, but others may take months or even years. The Boston University study found that restoration of white matter after the cessation of drinking appears to occur more quickly in women than in men.[3]

The fact that brain healing takes time helps explain the relapse risk for people in recovery from addiction. Despite the best of intentions, people often have trouble maintaining sobriety without the support of others. A comprehensive addiction treatment program can help patients understand the healing process and assemble a toolbox of skills to help them rebuild their lives while their bodies work on rebuilding their brains.

Continue Reading

- Pain Medication: Does It Increase Pain As Well as Cause Painkiller Addiction?
- Drug Addiction Profiled on Deadliest Catch
- How LSD Addiction Affects the Brain

Sources:

[1] Gravagna, Nicole. "How Does Addiction Physically Change The Brain?" *Forbes*, August 22, 2017.

[2] "Could brain abnormalities cause antisocial behavior and drug abuse in boys?" *Science Daily*, September 27, 2010.

[3] Seligson, Susan. "Why Alcoholics' Gender Matters." *BU Today*, November 21, 2013.

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The addicted human brain: insights from imaging studies

Nora D. Volkow,[1,2] Joanna S. Fowler,[3] and Gene-Jack Wang[1]

Imaging studies have revealed neurochemical and functional changes in the brains of drug-addicted subjects that provide new insights into the mechanisms underlying addiction. Neurochemical studies have shown that large and fast increases in dopamine are associated with the reinforcing effects of drugs of abuse, but also that after chronic drug abuse and during withdrawal, brain dopamine function is markedly decreased and these decreases are associated with dysfunction of prefrontal regions (including orbitofrontal cortex and cingulate gyrus). The changes in brain dopamine function are likely to result in decreased sensitivity to natural reinforcers since dopamine also mediates the reinforcing effects of natural reinforcers and on disruption of frontal cortical functions, such as inhibitory control and salience attribution. Functional imaging studies have shown that during drug intoxication, or during craving, these frontal regions become activated as part of a complex pattern that includes brain circuits involved with reward (nucleus accumbens), motivation (orbitofrontal cortex), memory (amygdala and hippocampus), and cognitive control (prefrontal cortex and cingulate gyrus). Here, we integrate these findings and propose a model that attempts to explain the loss of control and compulsive drug intake that characterize addiction. Specifically, we propose that in drug addiction the value of the drug and drug-related stimuli is enhanced at the expense of other reinforcers. This is a consequence of conditioned learning and of the resetting of reward thresholds as an adaptation to the high levels of stimulation induced by drugs of abuse. In this model, during exposure to the drug or drug-related cues, the memory of the expected reward results in over-activation of the reward and motivation circuits while decreasing the activity in the cognitive control circuit. This contributes to an inability to inhibit the drive to seek and consume the drug and results in compulsive drug

intake. This model has implications for therapy, for it suggests a multi-prong approach that targets strategies to decrease the rewarding properties of drugs, to enhance the rewarding properties of alternative reinforcers, to interfere with conditioned-learned associations, and to strengthen cognitive control in the treatment of drug addiction.

Introduction

Addiction is a disorder that involves complex interactions between biological and environmental variables (1). This has made treatment particularly elusive, since attempts to categorize addiction have usually concentrated on one level of analysis. Attempts to understand and treat addiction as a purely biological or a purely environmental problem have not been very successful. Recently, important discoveries have increased our knowledge about how drugs of abuse affect biological factors such as genes, protein expression, and neuronal circuits (2, 3); however, much less is known about how these biological factors affect human behavior. Nor do we know much about how environmental factors affect these biological factors and how these in turn alter behavior. Relatively new imaging technologies such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have provided new ways to investigate how the biological factors integrate with one another, how they relate to behavior, and how biological and environmental variables interact in drug addiction (Figure (Figure11).

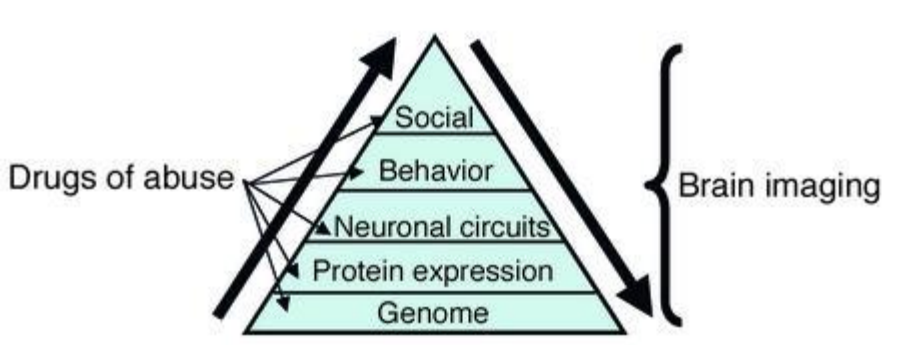

Figure 1

Drugs of abuse have effects at multiple biological and environmental levels. The environmental level is identified as “social,” since this is the most relevant of the environmental factors that influence drug abuse in humans. Imaging techniques allow one to assess the effects of drugs of abuse at the protein and the brain circuit levels and to assess how these effects relate to behavior. Imaging also offers a way to start to assess the impact of environmental factors on these biological levels, as well as the impact of gene polymorphisms on protein expression and brain function.

PET imaging is based on the use of radiotracers labeled with short-lived positron-emitting isotopes (carbon-11, oxygen-15, nitrogen-13, and fluorine-18), which it can measure at very low concentrations (nanomolar to picomolar range) (4). Therefore, PET can be used to measure labeled compounds that selectively bind to specific receptors, transporters, or enzyme types at concentrations that do not perturb function (Figure

(Figure2).2). fMRI is based on the measurement of the changes in magnetic properties in neuronal tissue (4). It is generally believed that the activation signal generated from fMRI results from differences in the magnetic properties of oxygenated versus deoxygenated hemoglobin (blood oxygen level dependent contrast). During activation of a brain region there is an excess of arterial blood delivered into the area, with concomitant changes in the ratio of deoxyhemoglobin to oxyhemoglobin.

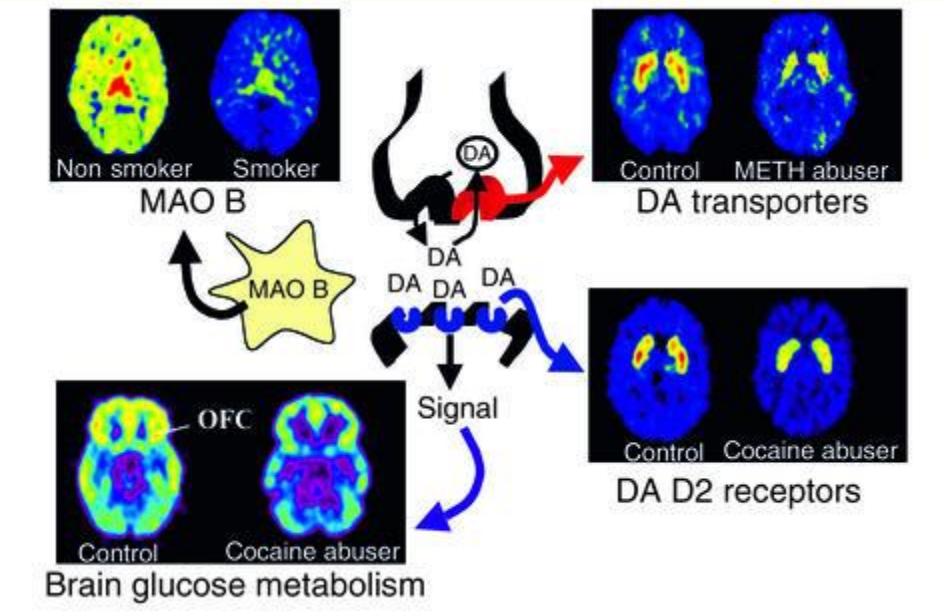

Figure 2

Images obtained with PET (axial sections) that show the effects of chronic drug exposure on various proteins involved in dopamine (DA) neurotransmission and on brain function (as assessed by brain glucose metabolism). While some effects are common to many drugs of abuse, such as decreases in DA D2 receptors in striatal neurons and decreased metabolic activity in the orbitofrontal cortex (OFC), others are more specific. These include the decrease in DA transporters in striatum in methamphetamine (METH) abusers (possibly the result of neurotoxicity to DA terminals) and the decrease in brain monoamine oxidase B (MAO B; the enzyme involved in DA metabolism) in cigarette smokers. The rainbow scale was used to code the PET images; radiotracer concentration is displayed from higher to lower as red > yellow > green > blue. Images from methamphetamine use are adapted from ref. 61. Images from smokers are adapted with permission from ref. 62.

Most PET studies of drug addiction have concentrated on the brain dopamine (DA) system, since this is considered to be the neurotransmitter system through which most drugs of abuse exert their reinforcing effects (5). A reinforcer is operationally defined as an event that increases the probability of a subsequent response, and drugs of abuse are considered to be much stronger reinforcers than natural reinforcers (e.g., sex and food) (6).The brain DA system also regulates motivation and drive for everyday activities (7). These imaging studies have revealed that acute and chronic drug

consumption have different effects on proteins involved in DA synaptic transmission (Figure (Figure2).2). Whereas acute drug administration increases DA neurotransmission, chronic drug consumption results in a marked decrease in DA activity, which persists months after detoxification and which is associated with deregulation of frontal brain regions (8). PET and MRI studies have characterized the brain areas and circuits involved in various states of the drug addiction process (intoxication, withdrawal, and craving) and have linked the activity in these neural circuits to behavior (Figure (Figure3).3). Acute drug intoxication results in a complex and dynamic pattern of activation and deactivation that includes regions neuroanatomically connected with the DA system and known to be involved in reward, memory, motivation/drive, and control (9, 10). The same imaging methods have been used to demonstrate how environmental factors can influence these neuronal circuits, which in turn affect behavior related to drug addiction (e.g., drug consumption). For example, a recent study in nonhuman primates showed that social status affects DA D2 receptor expression in the brain, which in turn affects the propensity for cocaine self-administration (11) (Figure (Figure44).

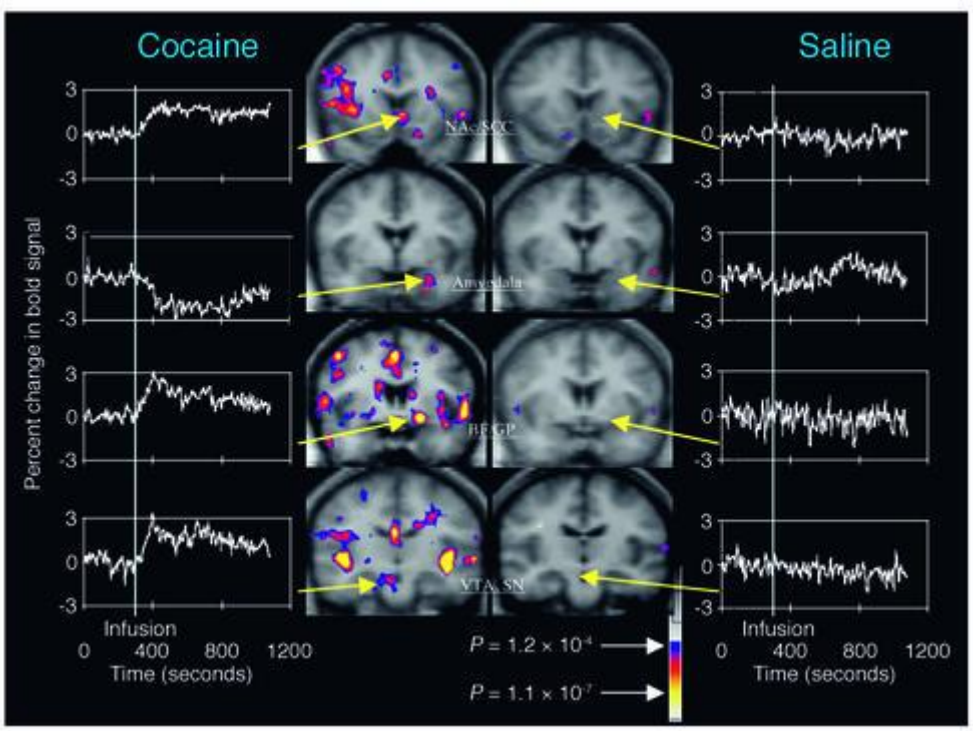

Figure 3

Images of coronal sections obtained with fMRI, showing areas of brain activation and deactivation during cocaine intoxication compared with those after saline administration. During intoxication there is a complex pattern of activation and/or deactivation that includes the ventral tegmental area (VTA) and the substantia nigra (SN), where DA cells are located, as well as regions involved with reward (nucleus accumbens, NAc; basal forebrain, BF; globus pallidus, GP), with memory (amygdala), and with motivation (subcallosal cortex, SCC). The color scale indicates the level of significance (*P* value) of

the change in activation of the bold signal. Reproduced with permission from *Neuron* (9).

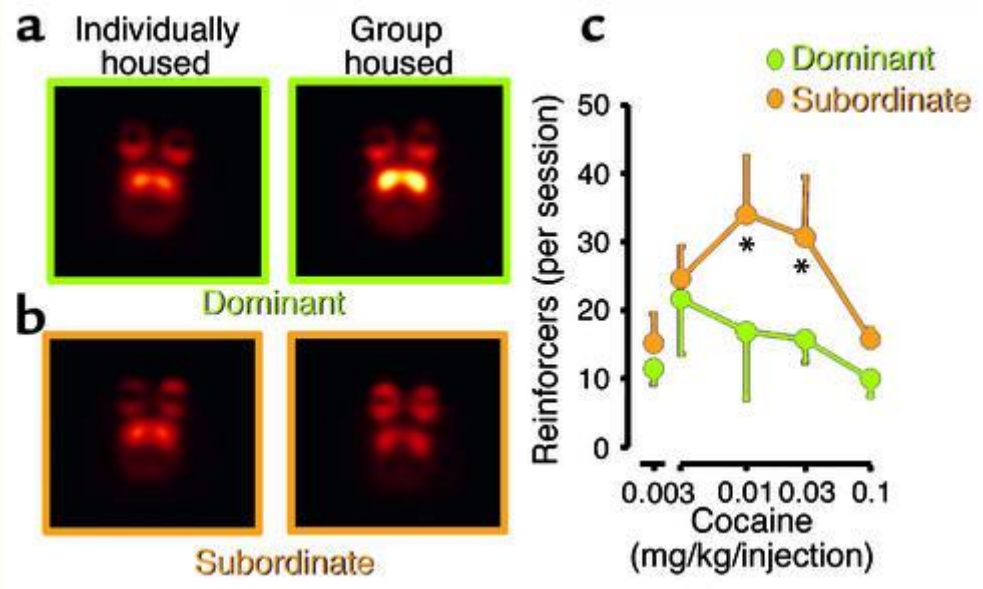

Figure 4

Images of axial sections obtained with PET, showing DA D2 receptors in nonhuman primates that were initially tested while housed in separate cages and then retested after being housed in a group. Animals that became dominant when placed in a group (**a**) showed increased numbers of DA D2 receptors in striatum, whereas subordinate animals (**b**) did not. (**c**) The levels of cocaine administration in the subordinate and the dominant animals. Note the much lower intake of cocaine by dominant animals which possessed higher numbers of DA D2 receptors. The temperature scale was used to code the PET images; radiotracer concentration is displayed from higher to lower as yellow > red. Asterisks indicate significant differences in drug intake between groups. Adapted with permission from ref. 11.

Here we analyze the results from our imaging program in drug addiction, and from the rich literature, and integrate this body of knowledge with preclinical findings to develop a model that could explain the loss of control and compulsive drug intake observed in the addicted individual.

Drug addiction involves multiple brain circuits

The aforementioned model proposes a network of four circuits involved in drug abuse and addiction: (a) reward, located in the nucleus accumbens (NAc) and the ventral pallidum; (b) motivation/drive, located in the orbitofrontal cortex (OFC) and the subcallosal cortex; (c) memory and learning, located in the amygdala and the hippocampus; and (d) control, located in the prefrontal cortex and the anterior cingulate gyrus (CG) (Figure (Figure5).5). These four circuits receive direct innervations from DA neurons but are also connected with one another through direct or indirect projections

(mostly glutamatergic). Though we have identified specific brain regions associated with each circuit, we have realized that other brain regions are involved in these circuits (e.g., the thalamus and insula), that one region may participate in more than one circuit (e.g., the CG in both control and motivation/drive circuits), and that other brain regions (e.g., the cerebellum) and circuits (e.g., attention and emotion circuits) are likely to be affected in drug addiction. Though our model focuses on DA, it is evident from preclinical studies that modifications in glutamatergic projections mediate many of the adaptations observed with addiction (12). Unfortunately, the lack of radiotracers available to image glutamate function in the human brain has precluded its investigation in drug-addicted subjects.

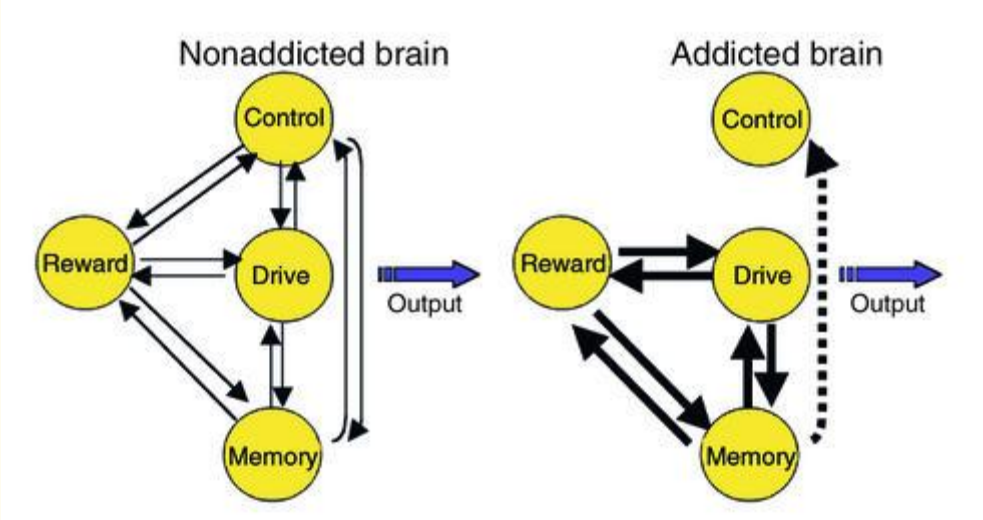

Figure 5

Model proposing a network of four circuits involved with addiction: reward, motivation/drive, memory, and control. These circuits work together and change with experience. Each is linked to an important concept: saliency (reward), internal state (motivation/drive), learned associations (memory), and conflict resolution (control). During addiction, the enhanced value of the drug in the reward, motivation, and memory circuits overcomes the inhibitory control exerted by the prefrontal cortex, thereby favoring a positive-feedback loop initiated by the consumption of the drug and perpetuated by the enhanced activation of the motivation/drive and memory circuits.

We propose that the pattern of activity in the four-circuit network outlined in Figure Figure55 influences how an individual makes choices among behavioral alternatives. These choices are influenced systematically by the reward, memory, motivation, and control circuits. The response to a stimulus is affected by its momentary saliency — i.e., expected reward, which is processed in part by DA neurons projecting into the NAc (13) — in a hierarchical matrix where the saliency value of stimuli changes as a function of the context and the previous experience of the individual. If the individual has been previously exposed to the stimulus, its saliency value is affected by memory, processed in part by the amygdala and hippocampus. Memories are stored as associations between the stimulus and the positive (pleasant) or negative (aversive) experience it

elicited and is facilitated by DA activation (14). The value of the stimulus is weighted against that of other alternative stimuli and changes as a function of the internal needs of the individual, which are processed in part by the OFC (15, 16). For example, the saliency value of food is increased by hunger but decreased by satiety. The stronger the saliency value of the stimulus, which is in part conveyed by the prediction of reward from previously memorized experiences, the greater the activation of the motivational circuit and the stronger the drive to procure it. The cognitive decision to act (or not) to procure the stimulus is processed in part by the prefrontal cortex and the CG (17).

The model proposes that, in the addicted subject, the saliency value of the drug of abuse and its associated cues is enhanced in the reward and motivation/drive circuits but that of other reinforcers is markedly decreased. The enhanced saliency value of the drug of abuse is initiated partly by the much higher intrinsic reward properties of drugs of abuse: increases in DA induced by drugs in the NAc are three- to fivefold higher than those of natural reinforcers (7). Another cause of the enhanced saliency is the lack of habituation of drugs of abuse as compared with that of natural reinforcers (18). It is postulated that the high reward value of drugs leads to a resetting of reward thresholds, which then results in decreased sensitivity to the reinforcing properties of naturally occurring stimuli (19). Through conditioned learning and a lack of competition by other reinforcers, acquisition of the drug becomes the main motivational drive for the individual. We hypothesize that, during intoxication, the qualitative difference in activity in the DA-regulated reward circuit (greater and longer-lasting activation compared with the activation by nondrug stimuli) (18) produces a corresponding over-activation of the motivational/drive and memory circuits, which deactivate and remove the control exerted by the frontal cortex. Without the inhibitory control, a positive-feedback loop is set forth that results in compulsive drug intake (Figure (Figure5).5). Because the interactions between the circuits are bidirectional, the activation of the network during intoxication serves to further strengthen the saliency value of the drug.

Reward circuit in drug addiction

The reinforcing effects of drugs during intoxication create an environment that, if perpetuated, triggers the neuronal adaptations that result in addiction. Imaging studies in drug abusers as well as non–drug abusers have shown that drugs of abuse increase the extracellular concentration of DA in the striatum (where the NAc is located) and that these increases were associated with their reinforcing effects. The subjects who had the greatest increases in DA were the ones who experienced drug effects such as “high,” “rush,” or “euphoria” most intensely (20–22). These studies also showed that the reinforcing effects appeared to be associated not only with the magnitude but also with the abruptness of the DA increase. Thus, for an equivalent increase in DA, the drug was experienced as reinforcing when it was injected intravenously (21), which leads to fast drug uptake in the brain and presumably very fast changes in DA concentration, but not when it was given orally (23), which leads to a slow rate of brain uptake and presumably slow increases in DA concentration. The dependency of the reinforcing effects of drugs on fast and large increases in DA concentration is reminiscent of the changes in DA concentration induced by phasic DA cell firing (fast-burst firing > 30 Hz) (6), which also leads to fast changes in DA concentration and whose function is to highlight the

saliency of stimuli (24). This contrasts with tonic DA cell firing (slow firing at frequencies around 5 Hz) (6), which maintains base-line steady-state DA levels and whose function is to set the overall responsiveness of the DA system. This led us to speculate that the ability of drugs of abuse to induce changes in DA concentration that mimic but exceed those produced by phasic DA cell firing results in over-activation of the neuronal processes that highlight saliency, and that this is one of the relevant variables underlying their high reinforcing value.

However, studies show that increases in DA concentration during intoxication occur in both addicted and non-addicted subjects, so this by itself cannot explain the process of addiction. Since drug addiction requires chronic drug administration, we suggest that addiction results from the repeated perturbation of reward circuits (marked DA increases followed by DA decreases) and the consequent disruption of the circuits that it regulates (motivation/drive, memory/learning, and control). Indeed, imaging studies in drug-addicted subjects have consistently shown long-lasting decreases in the numbers of DA D2 receptors in drug abusers compared with controls (Figure (Figure2)2) (reviewed in ref. 8). In addition, studies have shown that cocaine abusers also have decreased DA cell activity, as evidenced by reduced DA release in response to a pharmacological challenge with a stimulant drug (25). We postulate that the decrease in the number of DA D2 receptors, coupled with the decrease in DA cell activity, in the drug abusers would result in a decreased sensitivity of reward circuits to stimulation by natural reinforcers. This decreased sensitivity would lead to decreased interest in ordinary (day-to-day) environmental stimuli, possibly predisposing subjects for seeking drug stimulation as a means to temporarily activate these reward circuits. Imaging studies provide evidence of disrupted sensitivity to natural reinforcers in addiction. For example, in a study by Martin-Solch and colleagues (25), the meso-striatal and meso-corticolimbic circuits of opiate addicts were not activated in response to natural reinforcers, whereas they were in controls subjects. Similarly, in a second study by the same group, DA-regulated reward centers in tobacco smokers failed to activate in response to monetary reward (26). Interestingly, decreased sensitivity of reward circuits to acute alcohol administration has also been documented in cocaine abusers compared with control subjects (27). These findings suggest an overall reduction in the sensitivity of reward circuits in drug-addicted individuals to natural reinforcers, but also possibly to drugs besides the one to which they are addicted.

Motivation/drive circuit in addiction

We postulate that, during addiction, the value of the drug as a reinforcer is so much greater than that of any natural reinforcer that these can no longer compete as viable alternative choices, and the enhanced saliency value of the drug becomes fixed. This contrasts with natural reinforcers, whose saliency is momentary and decreases with exposure to the reinforcer (18) or with the presentation of an alternative, more appealing reinforcer. One area of the brain that is involved in shifting the relative value of reinforcers is the OFC (15, 16).

Imaging studies have provided evidence of disruption of the OFC during addiction (reviewed in ref. 28) (Figure (Figure2).2). The OFC appears to be hypoactive in drug-

addicted subjects tested during withdrawal (29, 30); we postulate that this results from the lack of stimulation by salient stimuli during detoxification. In contrast, in active cocaine abusers, the OFC has been shown to be hypermetabolic in proportion to the intensity of the craving experienced by the subjects (31). We therefore postulated that exposure to the drug or drug-related stimuli in the withdrawal state reactivates the OFC and results in compulsive drug intake. Indeed, activation of the OFC has been reported during drug intoxication in drug-addicted, but not in non–drug-addicted, subjects, and the level of activation predicted the intensity of drug-induced craving (32, 33). Similarly, activation of the OFC has been reported during exposure to drug-related cues when these elicit craving (reviewed in ref. 28). Since increased OFC activation has been associated with compulsive disorders (reviewed in ref. 34), we postulated that the activation of the OFC in addicted subjects contributes to the compulsive drug intake. Indeed, preclinical studies have shown that damage of the OFC results in a behavioral compulsion to procure the reward even when it is no longer reinforcing (16). This is consistent with the accounts of drug addicts who claim that once they start taking the drug they cannot stop, even when the drug is no longer pleasurable. Since the OFC also processes information associated with the prediction of reward (15), its activation during cue exposure could signal reward prediction, which could then be experienced as craving by the addicted subject.

In detoxified drug abusers, the decreased activity in the OFC is associated with reductions in the numbers of DA D2 receptors in striatum (35, 36). Since DA D2 receptors transmit reward signals into the OFC, this association could be interpreted as a disruption of the OFC, secondary to changes in striatal DA activity (such as lack of stimulation during withdrawal and enhanced stimulation with exposure to drugs or drug-related cues). However, since striatal-frontal connections are bidirectional, this association could also reflect the disruption of the OFC, which then deregulates DA cell activity.

Learning/memory circuit in addiction

The relevance of learning and memory to addiction is made evident by the pernicious effect that a place, a person, or a cue that brings back memories of the drug can have on the addict who is trying to stay clean. These factors trigger an intense desire for the drug (a craving) and, not infrequently, relapse. Multiple memory systems have been proposed in drug addiction, including conditioned-incentive learning (mediated in part by the NAc and the amygdala), habit learning (mediated in part by the caudate and the putamen), and declarative memory (mediated in part by the hippocampus) (reviewed in ref. 37). Through conditioned-incentive learning, the neutral stimuli, coupled with the drug of abuse, acquire reinforcing properties and motivational salience even in the absence of the drug. Through habit learning, well-learned sequences of behavior are elicited automatically by the appropriate stimuli. Finally, declarative memory is related to the learning of affective states in relationship to drug intake.

Memory circuits are likely to influence the effects of the drug during intoxication, since they set the expectations of the drug's effects in the addicted subject (38). Activation of regions linked with memory has been reported during drug intoxication (9, 10) and

during craving induced by drug exposure, video, or recall (39–42). Also, studies in drug abusers during withdrawal have shown evidence of decreased D2 receptor expression and decreased DA release in the dorsal striatum (25). In animal studies, the drug-induced changes in the dorsal striatum are observed after longer drug exposures than those observed in the NAc and have been interpreted to reflect further progression into the addicted state (43). This is relevant because involvement of the dorsal striatum, which is a region associated with habit learning, indicates that in drug addiction the routine associated with drug consumption may be triggered automatically by exposure to the drug or drug-related cues (44).

Control circuit in addiction

One of the most consistent findings from imaging studies is that of abnormalities in the prefrontal cortex, including the anterior CG, in drug-addicted subjects (reviewed in ref. 45). The prefrontal cortex is involved in decision making and in inhibitory control (reviewed in ref. 46). Thus its disruption could lead to inadequate decisions that favor immediate rewards over delayed but more favorable responses. It could also account for the impaired control over the intake of the drug even when the addicted subject expresses the desire to refrain from taking the drug (45). Thus, one might expect that the disruptions of self-monitoring and decision-making processes that are observed in drug-addicted subjects (47, 48) are in part related to disrupted prefrontal functions. Moreover, preclinical studies show that chronic administration of cocaine or amphetamine results in a significant increase in dendritic branching and the density of dendritic spines in the prefrontal cortex (49). These changes in synaptic connectivity could be involved in the changes in decision making, judgment, and cognitive control that occur during addiction. Indeed, imaging studies have shown evidence of changes in prefrontal activation during a working-memory task in smokers compared with ex-smokers (50).

We propose that disruption of the prefrontal cortex could lead to loss of self-directed/willed behavior in favor of automatic sensory-driven behavior (45). Moreover, the disruption of self-controlled behavior is likely to be exacerbated during drug intoxication from the loss of inhibitory control that the prefrontal cortex exerts over the amygdala (51). The inhibition of top-down control would release behaviors that are normally kept under close monitoring and would simulate stress-like reactions in which control is inhibited and stimulus-driven behavior is facilitated (45).

Vulnerability to drug addiction

A challenging problem in the neurobiology of drug addiction is to understand why some individuals become addicted to drugs while others do not. The model we propose offers some guidance as to specific disruptions that could make a subject more or less vulnerable to addiction. For example, one could hypothesize that decreased sensitivity of reward circuits to natural reinforcers, decreased activity of control circuits, or an increased sensitivity of memory/learning or motivation/drive circuits to drug or drug-related stimuli could make an individual more vulnerable to addiction.

In fact, imaging studies have provided evidence that differences in reward circuits may be one of the mechanisms underlying the variability in responsiveness to drugs of abuse, which in turn could influence vulnerability. These studies assessed the extent to which the variability in the number of DA D2 receptors in non–drug-abusing subjects affected their sensitivity to stimulant drugs (52). The data showed that subjects with low numbers of DA D2 receptors tended to describe the effects of the stimulant drug methylphenidate as pleasant, whereas subjects with high numbers of DA D2 receptors tended to describe it as unpleasant (Figure (Figure6).6). Another study documented that the numbers of DA D2 receptors predicted how much subjects liked the effects of methylphenidate (53). These findings suggest that one of the mechanisms underlying the differences between subjects in their vulnerability to stimulant abuse may be the variability in the expression of DA D2 receptors. Subjects with low numbers of D2 receptors may be at higher risk of abusing stimulant drugs than those with high numbers of D2 receptors, in whom drugs such as methylphenidate may produce unpleasant effects that limit its abuse. A causal association between DA D2 receptor numbers and propensity to self-administer drugs was corroborated by a parallel preclinical study that showed that insertion of the DA D2 receptor gene via a viral vector to increase DA D2 receptor expression in the NAc of rats previously trained to self-administer alcohol resulted in marked reductions in alcohol intake (54). Alcohol intake recovered as the number of DA D2 receptors returned to baseline levels. These results could be taken as indirect evidence of a protective role of high DA D2 receptor numbers against drug abuse. Baseline levels of DA D2 receptors in the brain, which have been shown to be affected by stress (55) and social hierarchy (11), provide a molecular mechanism that could explain the influence of the environment and genetics on predisposition to drug abuse.

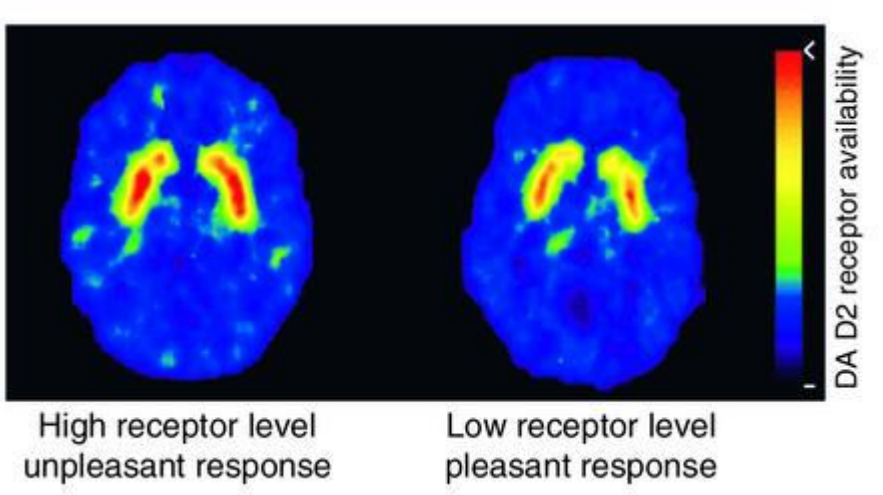

Figure 6

Images of axial sections obtained with PET to measure the numbers of DA D2 receptors in subjects who reported the effects of the stimulant drug methylphenidate as pleasant versus those that reported its effects as unpleasant. Subjects with high numbers of DA D2 receptors tended to report the effects of methylphenidate as unpleasant, whereas subjects with low numbers of DA D2 receptors tended to report it as pleasant. The rainbow scale

was used to code the PET images; radiotracer concentration is displayed from higher to lower as red > yellow > green > blue. Adapted with permission from ref. 53.

Recently, imaging studies showed that offspring of alcoholic families who were considered to be at high risk for alcoholism showed smaller amygdala volumes in comparison with control subjects (56). Moreover, the volume of the amygdala was associated with the amplitude of the P300 in the evoked potential (wave occurring between 300 and 500 ms after a rare target stimulus), which is considered to be a phenotypic marker for vulnerability to alcoholism. Also, a recent imaging study reported structural changes in the OFC of cocaine-addicted subjects (57), and the possibility was discussed that this might have preceded drug use and might have made these subjects more vulnerable to addiction.

Access to transgenic and knockout animals now provides a means to directly evaluate the role that specific genes may play in vulnerability to, or protection against, drug abuse and addiction (58). Thus, information from imaging studies regarding abnormalities in specific proteins in the brains of drug-addicted subjects (e.g., DA D2 receptors and monoamine oxidase B) can now be tested in preclinical models to determine whether these abnormalities reflect changes that preceded drug use and are genetically determined, or whether they are a consequence of chronic drug use.

Conclusion

Here we provide a model that conceptualizes addiction as a state initiated by the qualitatively different and larger reward value of the drug, which triggers a series of adaptations in the reward, motivation/drive, memory, and control circuits of the brain. These changes result in an enhanced and permanent saliency value for the drug, and in the loss of inhibitory control, favoring the emergence of compulsive drug administration. The model has treatment implications, for it suggests strategies to combat drug addiction — specifically (a) interventions to decrease the rewarding value of drugs, such as pharmacological treatments that interfere with the drug's reinforcing effects as well as treatments that make the effects unpleasant; (b) interventions to increase the value of nondrug reinforcers, such as pharmacological and behavioral treatments that increase sensitivity to natural reinforcers and establish alternative reinforcing behaviors; (c) interventions to weaken learned drug responses, such as behavioral treatments to extinguish the learned positive associations with the drug and drug cues but also promote differential reinforcement of other behaviors; and (d) interventions to strengthen frontal control, such as cognitive therapy. The model also highlights the need for therapeutic approaches that include pharmacological as well as behavioral interventions in the treatment of drug addiction (59).

This analysis brings to light the paucity of PET radiotracers currently available for use in imaging of the human brain. Further research on the development of radiotracers that can be used to target other neurotransmitter systems affected by drugs of abuse (e.g., glutamate and γ-aminobutyric acid) will in the future provide a more complete picture of the neurochemical changes that underlie drug addiction. Moreover, access to a wider array of radiotracers will enable researchers to start to investigate the role that gene

polymorphisms may play in protein expression, and how this in turn relates to behavioral responses to drugs of abuse (60).

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Footnotes

Conflict of interest: The authors have declared that no conflict of interest exists.

Nonstandard abbreviations used: positron emission tomography (PET); functional magnetic resonance imaging (fMRI); dopamine (DA); nucleus accumbens (NAc); orbitofrontal cortex (OFC); cingulate gyrus (CG).

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