CHAPTER 2.
THE NEUROBIOLOGY OF SUBSTANCE USE, MISUSE, AND ADDICTION

Chapter 2 Preview

A substantial body of research has accumulated over several decades and transformed our understanding of substance use and its effects on the brain. This knowledge has opened the door to new ways of thinking about prevention and treatment of substance use disorders.

This chapter describes the neurobiological framework underlying substance use and why some people transition from using or misusing alcohol or drugs to a substance use disorder—including its most severe form, addiction. The chapter explains how these substances produce changes in brain structure and function that promote and sustain addiction and contribute to relapse. The chapter also addresses similarities and differences in how the various classes of addictive substances affect the brain and behavior and provides a brief overview of key factors that influence risk for substance use disorders.

An Evolving Understanding of Substance Use Disorders

Scientific breakthroughs have revolutionized the understanding of substance use disorders. For example, severe substance use disorders, commonly called *addictions*, were once viewed largely as a moral failing or character flaw, but are now understood to be chronic illnesses characterized by clinically significant impairments in health, social function, and voluntary control over substance use.[3] Although the mechanisms may be different, addiction has many features in common with disorders such as diabetes, asthma, and hypertension. All of these disorders are chronic, subject to relapse, and influenced by genetic, developmental, behavioral, social, and environmental factors. In all of these disorders, affected individuals may have difficulty in complying with the prescribed treatment.[4]

This evolving understanding of substance use disorders as medical conditions has had important implications for prevention and treatment. Research demonstrating that addiction is driven by changes in the brain has helped to reduce the negative attitudes associated with substance use disorders and provided support for integrating treatment for substance use disorders into mainstream health care. Moreover, research on the basic neurobiology of addiction has already resulted in several effective

KEY FINDINGS*

- Well-supported scientific evidence shows that addiction to alcohol or drugs is a chronic brain disease that has potential for recurrence and recovery.
- Well-supported evidence suggests that the addiction process involves a three-stage cycle: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. This cycle becomes more severe as a person continues substance use and as it produces dramatic changes in brain function that reduce a person's ability to control his or her substance use.
- Well-supported scientific evidence shows that disruptions in three areas of the brain are particularly important in the onset, development, and maintenance of substance use disorders: the basal ganglia, the extended amygdala, and the prefrontal cortex. These disruptions: (1) enable substance-associated cues to trigger substance seeking (i.e., they increase incentive salience); (2) reduce sensitivity of brain systems involved in the experience of pleasure or reward, and heighten activation of brain stress systems; and (3) reduce functioning of brain executive control systems, which are involved in the ability to make decisions and regulate one's actions, emotions, and impulses.
- Supported scientific evidence shows that these changes in the brain persist long after substance use stops. It is not yet known how much these changes may be reversed or how long that process may take.
- Well-supported scientific evidence shows that adolescence is a critical "at-risk period" for substance use and addiction. All addictive drugs, including alcohol and marijuana, have especially harmful effects on the adolescent brain, which is still undergoing significant development.

* Well-supported: when evidence is derived from multiple rigorous human and nonhuman studies; Supported: when evidence is derived from rigorous but fewer human and nonhuman studies.

medications for the treatment of alcohol, opioid, and nicotine use disorders, and clinical trials are ongoing to test other potential new treatments.[5]

All addictive substances have powerful effects on the brain. These effects account for the euphoric or intensely pleasurable feelings that people experience during their initial use of alcohol or other substances, and these feelings motivate people to use those substances again and again, despite the risks for significant harms.

FOR MORE ON THIS TOPIC

See the section on *"Factors that Increase Risk for Substance Use, Misuse, and Addiction" later in this chapter.*

As individuals continue to misuse alcohol or other substances, progressive changes, called *neuroadaptations,* occur in the structure and function of the brain. These neuroadaptations compromise brain function and also drive the transition from controlled, occasional substance use to chronic misuse, which can be difficult to control. Moreover, these brain changes endure long after an individual stops using substances. They may produce continued, periodic craving for the substance that can lead to relapse: More than 60 percent of people treated for a substance use disorder experience relapse within the first year after they are discharged from treatment,[4,6] and a person can remain at increased risk of relapse for many years.[7,8]

However, addiction is not an inevitable consequence of substance use. Whether an individual ever uses alcohol or another substance, and whether that initial use progresses to a substance use disorder of any severity, depends on a number of factors. These include: a person's genetic makeup and other individual

biological factors; the age when use begins; psychological factors related to a person's unique history and personality; and environmental factors, such as the availability of drugs, family and peer dynamics, financial resources, cultural norms, exposure to stress, and access to social support.[9] Some of these factors increase risk for substance use, misuse, and use disorders, whereas other factors provide buffers against those risks. Nonetheless, specific combinations of factors can drive the emergence and continuation of substance misuse and the progression to a disorder or an addiction.

FOR MORE ON THIS TOPIC

See Chapter 3 - *Prevention Programs and Policies.*

Conducting Research on the Neurobiology of Substance Use, Misuse, and Addiction

Until recently, much of our knowledge about the neurobiology of substance use, misuse, and addiction came from the study of laboratory animals. Although no animal model fully reflects the human experience, animal studies let researchers investigate addiction under highly controlled conditions that may not be possible or ethical to replicate in humans. These types of studies have greatly helped to answer questions about how particular genes, developmental processes, and environmental factors, such as stressors, affect substance-taking behavior.

KEY TERMS

Neurobiology. The study of the anatomy, function, and diseases of the brain and nervous system.

Neurobiology studies in animals have historically focused on what happens in the brain right after taking an addictive substance (this is called the acute impact), but research has shifted to the study of how ongoing, long-term (or chronic) substance use changes the brain. One of the main goals of this research is to understand at the most basic level the mechanisms through which substance use alters brain structure and function and drives the transition from occasional use to misuse, addiction, and relapse.[10]

A growing body of substance use research conducted with humans is complementing the work in animals. For example, human studies have benefited greatly from the use of brain-imaging technologies, such as magnetic resonance imaging (MRI) and positron emission tomography (PET) scans. These technologies allow researchers to "see" inside the living human brain so that they can investigate and characterize the biochemical, functional, and structural changes in the brain that result from alcohol and drug use. The technologies also allow them to understand how differences in brain structure and function may contribute to substance use, misuse, and addiction.

Animal and human studies build on and inform each other, and in combination provide a more complete picture of the neurobiology of addiction. The rest of this chapter weaves together the most compelling data from both types of studies to describe a neurobiological framework for addiction.

A Basic Primer on the Human Brain

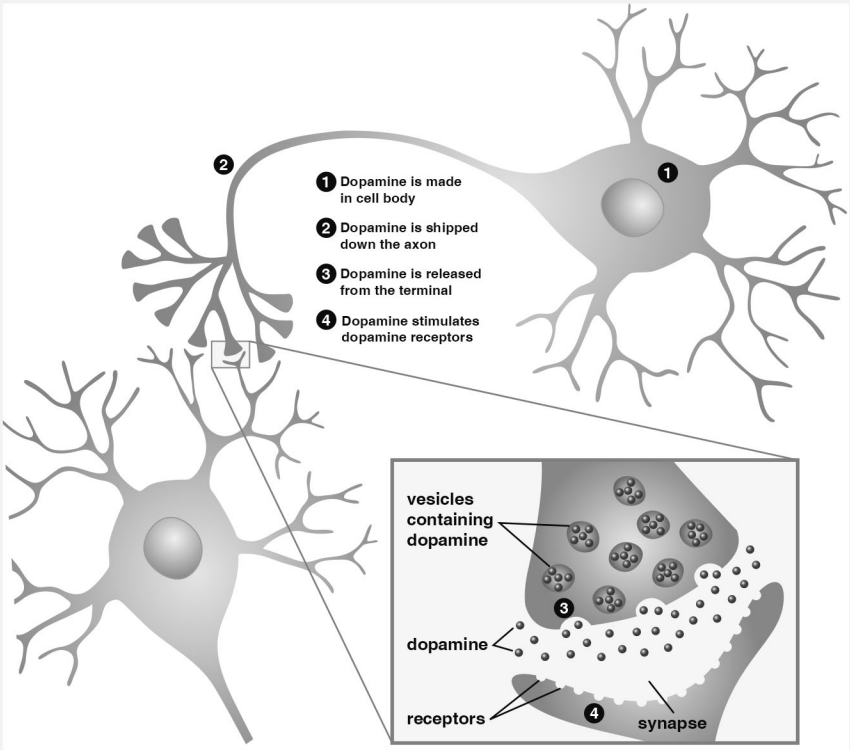
To understand how addictive substances affect the brain, it is important to first understand the basic biology of healthy brain function. The brain is an amazingly complex organ that is constantly at work. Within the brain, a mix of chemical and electrical processes controls the body's most basic functions, like breathing and digestion. These processes also control how people react to the multitudes of sounds, smells, and other sensory stimuli around them, and they organize and direct individuals' highest thinking and emotive powers so that they can interact with other people, carry out daily activities, and make complex decisions.

The brain is made of an estimated 86 billion nerve cells—called neurons—as well as other cell types. Each neuron has a cell body, an axon, and dendrites (Figure 2.1). The cell body and its nucleus control the neuron's activities. The axon extends out from the cell body and transmits messages to other neurons. Dendrites branch out from the cell body and receive messages from the axons of other neurons.

Neurons communicate with one another through chemical messengers called neurotransmitters. The neurotransmitters cross a tiny gap, or synapse, between neurons and attach to receptors on the receiving neuron. Some neurotransmitters are inhibitory—they make it less likely that the receiving neuron will carry out some action. Others are excitatory, meaning that they stimulate neuronal function, priming it to send signals to other neurons.

Neurons are organized in clusters that perform specific functions (described as networks or circuits). For example, some networks are involved with thinking, learning, emotions, and memory. Other networks communicate with muscles, stimulating them into action. Still others receive and interpret stimuli from the sensory organs, such as the eyes and ears, or the skin. The addiction cycle disrupts the normal functions of some of these neuronal networks.

Figure 2.1: A Neuron and its Parts

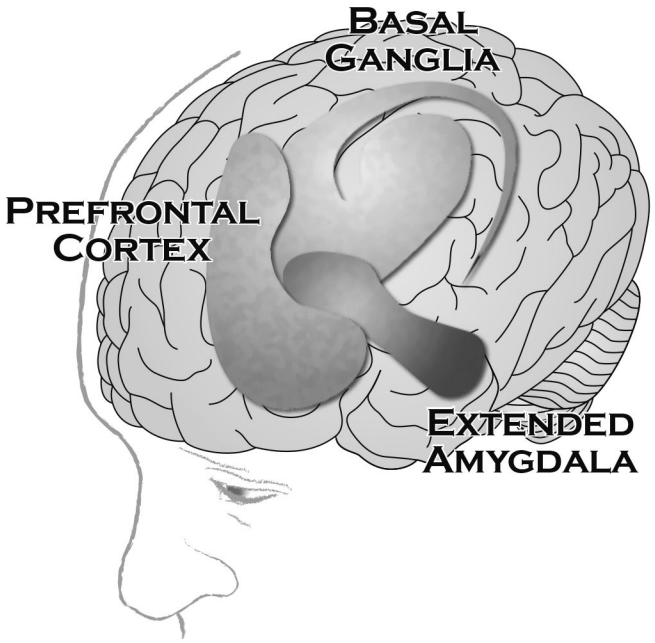


The Primary Brain Regions Involved in Substance Use Disorders

The brain has many regions that are interconnected with one another, forming dynamic networks that are responsible for specific functions, such as attention, self-regulation, perception, language, reward, emotion, and movement, along with many other functions. This chapter focuses on three regions that are the key components of networks that are intimately involved in the development and persistence of substance use disorders: the **basal ganglia**, the **extended amygdala**, and the **prefrontal cortex** (Figure 2.2). The basal ganglia control the rewarding, or pleasurable, effects of substance use and are also responsible for the formation of habitual substance taking. The extended amygdala is involved in stress and the feelings of unease, anxiety, and irritability that typically accompany substance withdrawal. The prefrontal cortex is involved in executive function (i.e., the ability to organize thoughts and activities, prioritize tasks, manage time, and make decisions), including exerting control over substance taking.

These brain areas and their associated networks are not solely involved in substance use disorders. Indeed, these systems are broadly integrated and serve many critical roles in helping humans and other animals survive. For example, when people engage in certain activities, such as consuming food or having sex, chemicals within the basal ganglia produce feelings of pleasure. This reward motivates individuals to continue to engage in these activities, thereby ensuring the survival of the species. Likewise, in the face of danger, activation of the brain's stress systems within the extended amygdala drives "fight or flight" responses. These responses, too, are critical for survival. As described in more detail below, these and other survival systems are "hijacked" by addictive substances.

Figure 2.2: Areas of the Human Brain that Are Especially Important in Addiction



The Basal Ganglia

The basal ganglia are a group of structures located deep within the brain that play an important role in keeping body movements smooth and coordinated. They are also involved in learning routine behaviors and forming habits. Two sub-regions of the basal ganglia are particularly important in substance use disorders:

- The nucleus accumbens, which is involved in motivation and the experience of reward, and
- The dorsal striatum, which is involved in forming habits and other routine behaviors.[11]

The Extended Amygdala

The extended amygdala and its sub-regions, located beneath the basal ganglia, regulate the brain's reactions to stress-including behavioral responses like "fight or flight" and negative emotions like unease, anxiety, and irritability. This region also interacts with the hypothalamus, an area of the brain that controls activity of multiple hormone-producing glands, such as the pituitary gland at the base of the brain and the adrenal glands at the top of each kidney. These glands, in turn, control reactions to stress and regulate many other bodily processes.[12]

The Prefrontal Cortex

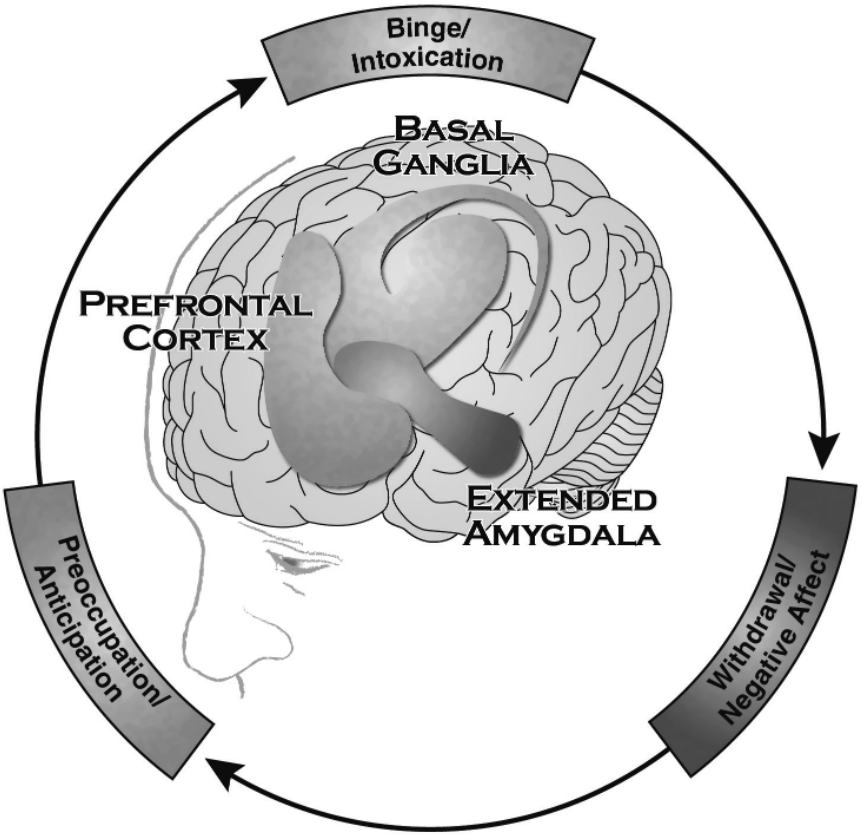
The prefrontal cortex is located at the very front of the brain, over the eyes, and is responsible for complex cognitive processes described as "executive function." Executive function is the ability to organize thoughts and activities, prioritize tasks, manage time, make decisions, and regulate one's actions, emotions, and impulses.[13]

The Addiction Cycle

Addiction can be described as a repeating cycle with three stages. Each stage is particularly associated with one of the brain regions described above—basal ganglia, extended amygdala, and prefrontal cortex (**Figure 2.3**).[10] This three-stage model draws on decades of human and animal research and provides a useful way to understand the symptoms of addiction, how it can be prevented and treated, and how people can recover from it.[14] The three stages of addiction are:

- **Binge/Intoxication**, the stage at which an individual consumes an intoxicating substance and experiences its rewarding or pleasurable effects;
- **Withdrawal/Negative Affect**, the stage at which an individual experiences a negative emotional state in the absence of the substance; and
- **Preoccupation/Anticipation**, the stage at which one seeks substances again after a period of abstinence.

Figure 2.3: The Three Stages of the Addiction Cycle and the Brain Regions Associated with Them



The three stages are linked to and feed on each other, but they also involve different brain regions, circuits (or networks), and neurotransmitters and result in specific kinds of changes in the brain. A person may go through this three-stage cycle over the course of weeks or months or progress through it several times in a day. There may be variation in how people progress through the cycle and the intensity with which they experience each of the stages. Nonetheless, the addiction cycle tends to intensify over time, leading to greater physical and psychological harm.[10]

The following sections describe each of the stages in more detail. But first, it is necessary to explain four behaviors that are central to the addiction cycle: impulsivity, positive reinforcement, negative reinforcement, and compulsivity.

For many people, initial substance use involves an element of impulsivity, or acting without foresight or regard for the consequences. For example, an adolescent may impulsively take a first drink, smoke a cigarette, begin experimenting with marijuana, or succumb to peer pressure to try a party drug. If the experience is pleasurable, this feeling positively reinforces the substance use, making the person more likely to take the substance again.

Another person may take a substance to relieve negative feelings such as stress, anxiety, or depression. In this case, the temporary relief the substance brings from the negative feelings negatively reinforces

substance use, increasing the likelihood that the person will use again. Importantly, positive and negative reinforcement need not be driven solely by the effects of the drugs. Many other environmental and social stimuli can reinforce a behavior. For example, the approval of peers positively reinforces substance use for some people. Likewise, if drinking or using drugs with others provides relief from social isolation, substance use behavior could be negatively reinforced.

The positively reinforcing effects of substances tend to diminish with repeated use. This is called tolerance and may lead to use of the substance in greater amounts and/or more frequently in an attempt to experience the initial level of reinforcement. Eventually, in the absence of the substance, a person may experience negative emotions such as stress, anxiety, or depression, or feel physically ill. This is called withdrawal, which often leads the person to use the substance again to relieve the withdrawal symptoms.

As use becomes an ingrained behavior, impulsivity shifts to compulsivity, and the primary drivers of repeated substance use shift from positive reinforcement (feeling pleasure) to negative reinforcement (feeling relief), as the person seeks to stop the negative feelings and physical illness that accompany withdrawal.[15] Eventually, the person begins taking the substance not to get "high," but rather to escape the "low" feelings to which, ironically, chronic drug use has contributed. Compulsive substance seeking is a key characteristic of addiction, as is the loss of control over use. Compulsivity helps to explain why many people with addiction experience relapses after attempting to abstain from or reduce use.

KEY TERMS

Impulsivity. An inability to resist urges, deficits in delaying gratification, and unreflective decision-making. It is a tendency to act without foresight or regard for consequences and to prioritize immediate rewards over long-term goals.[1]

Positive reinforcement. The process by which presentation of a stimulus such as a drug increases the probability of a response like drug taking.

Negative reinforcement. The process by which removal of a stimulus such as negative feelings or emotions increases the probability of a response like drug taking.

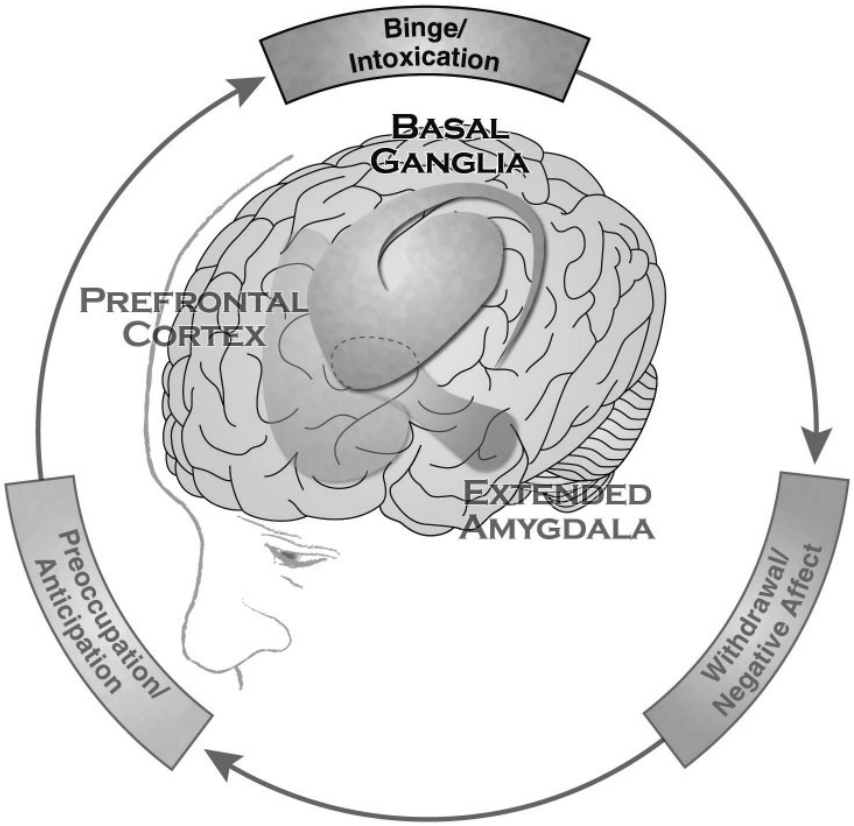
Compulsivity. Repetitive behaviors in the face of adverse consequences, and repetitive behaviors that are inappropriate to a particular situation. People suffering from compulsions often recognize that the behaviors are harmful, but they nonetheless feel emotionally compelled to perform them. Doing so reduces tension, stress, or anxiety.[1]

The following sections provide more detail about each of the three stages—binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation—and the neurobiological processes underlying them.

Binge/Intoxication Stage: Basal Ganglia

The binge/intoxication stage of the addiction cycle is the stage at which an individual consumes the substance of choice. This stage heavily involves the basal ganglia (**Figure 2.4**) and its two key brain sub-regions, the nucleus accumbens and the dorsal striatum. In this stage, substances affect the brain in several ways.

Figure 2.4: The Binge/Intoxication Stage and the Basal Ganglia



Addictive Substances "Hijack" Brain Reward Systems

All addictive substances produce feelings of pleasure. These "rewarding effects" positively reinforce their use and increase the likelihood of repeated use. The rewarding effects of substances involve activity in the nucleus accumbens, including activation of the brain's dopamine and opioid signaling system. Many studies have shown that neurons that release dopamine are activated, either directly or indirectly, by all addictive substances, but particularly by stimulants such as cocaine, amphetamines, and nicotine (**Figure 2.5**).[16] In addition, the brain's opioid system, which includes naturally occurring opioid molecules (i.e., endorphins, enkephalins, and dynorphins) and three types of opioid receptors (i.e., mu, delta, and kappa), plays a key role in mediating the rewarding effects of other addictive substances, including opioids and alcohol. Activation of the opioid system by these substances stimulates the nucleus accumbens directly or indirectly through the dopamine system. Brain imaging studies in humans show activation of dopamine and opioid neurotransmitters during alcohol and other substance use (including nicotine).[10,17] Other studies show that antagonists, or inhibitors, of dopamine and opioid receptors can block drug and alcohol seeking in both animals and humans.[14,18,19]

KEY TERMS

Antagonist. A chemical substance that binds to and blocks the activation of certain receptors on cells, preventing a biological response. Naloxone is an example of an opioid receptor antagonist.