CHAPTER ONE

What is Addiction?

Learning Objectives

- Be able to describe the clinical definition of addiction.
- Be able to recognize the phenomenology of addiction.
- Be able to explain how psychoactive substances are classified.
- Be able to characterize the brain disease model of addiction.
- Be able to understand the concept of behavioral addiction.

Introduction

According to the World Health Organization, there were 2 billion alcohol users, 1.3 billion smokers and 185 million drug users in the year 2000. This figure contributed to 12.4% of all deaths worldwide that year. Addiction does not discriminate. It affects both sexes, all races and all ages. However, the highest rate of addiction is in the adolescent to emerging-adult populations (ages 12–29 years) (UNODC, 2012). The high rate of substance use initiation during this period has the potential to change the tone for how the brain develops, given that this age period is when the brain undergoes critical maturation processes. Figure 1.1 illustrates brain development as a process consisting of gray matter reductions and cortical thinning that is then followed by increased white matter volume, connectivity and organization through adolescence and young adulthood (Giorgio *et al.*, 2010; Gogtay *et al.*, 2004; Hasan *et al.*, 2007; Lebel *et al.*, 2010; Shaw *et al.*, 2008).

Guided by multidisciplinary research in neuroscience, epidemiology, brain imaging and genetics, addiction is now understood to be a brain disease due to the changes it exerts on the brain. Like other brain diseases, addiction is best described using the three Ps: pervasive, persistent and pathological. Addiction is *pervasive* as it affects all aspects of the individual's life. Addiction is *persistent* as its effects persevere despite efforts by the individual. Last, addiction is *pathological* because the

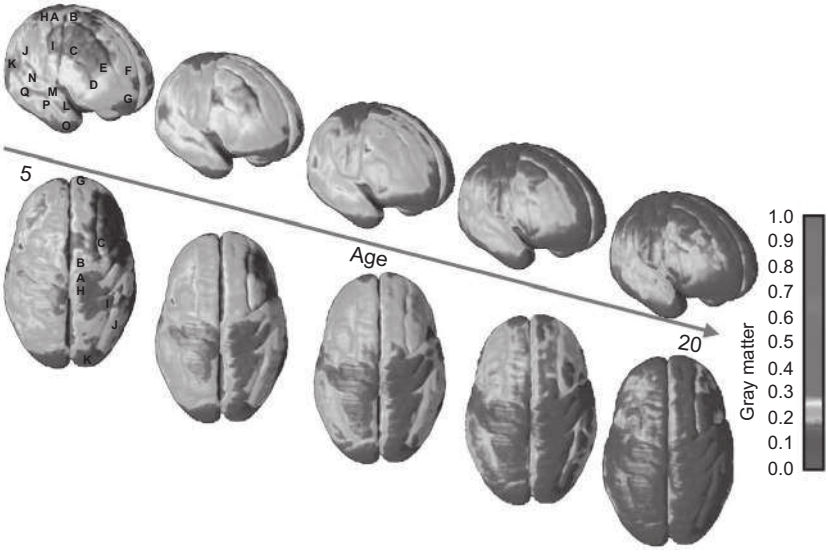

Figure 1.1 A longitudinal study demonstrating neuromaturational processes from 5 to 20 years of age. (From Gogtay *et al.*, 2004. © 2004 National Academy of Sciences, USA.) (A black and white version of this figure will appear in some formats. For the color version, please refer to the plate section.)

effects are uncontrollable. Thus, compulsive drug seeking and continued use despite negative consequences broadly characterize addiction.

From a clinical perspective, addiction is officially diagnosed via clinical interview using guidelines such as the *Diagnostic and Statistical Manual of Mental Disorders*, currently in its 5th edition (DSM-5) by the American Psychiatric Association or the *International Classification of Diseases* (ICD) published by the World Health Organization. According to the DSM-5, addiction is a chronic progressive disease with behavioral patterns that fall within a spectrum of severity. Thus, the DSM-5, implemented in 2014, refers to this broad spectrum as "substance use disorders" (SUDs).

In the USA, the Drug Enforcement Administration (DEA) organizes drugs within a schedule of drug classes that are based on risk for abuse and harm as well as acceptable medical use (Table 1.1). Schedule I drugs have the highest risk for abuse and harm and little to no medical benefit, while schedule V drugs have low potential for abuse. Schedule I drugs include heroin, lysergic acid diethylamide (LSD), cannabis, peyote, methaqualone, and 3,4-methylenedioxymethamphetamine (ecstasy). Furthermore, drugs of abuse are classified into categories based on their mechanism of

Table 1.1 2017 Schedule of Drugs according to the US DEA. The DEA classifies drugs into five distinct categories or schedules depending on the drug's acceptable medical use and the drug's abuse or dependency potential. Schedule I drugs have the highest potential for abuse and the potential to create severe psychological and/or physical dependence. Schedule V drugs represent the least potential for abuse.

Drug schedule	Classification meaning (defined by the DEA)	Drugs, substances, chemicals
Schedule I	No currently accepted medical use High potential for abuse	Heroin LSD Cannabis Ecstasy Methaqualone Peyote
Schedule II	High potential for abuse Severe dependence risk	Vicodin Cocaine Methamphetamine Methadone Dilaudid Demerol OxyContin Fentanyl Dexedrine Adderall Ritalin
Schedule III	Moderate to low potential for abuse Moderate to low dependence risk	Codeine Ketamine Anabolic Steroids Testosterone
Schedule IV	Low potential risk for abuse Low potential for dependence	Xanax Darvocet Valium Ativan Ambien Tramadol
Schedule V	Lower potential risk for abuse Lower potential risk for dependence	Robitussin Lyrica

action and behavioral effects: narcotics, cannabinoids, depressants, stimulants, hallucinogens and inhalants. For instance, some target specific receptors (e.g. cannabinoids) whereas others target multiple receptor systems (e.g. stimulants).

The Phenomenology of Substance Use Disorders

Addiction is often defined as compulsive drug seeking despite the negative consequences related with the substance use. Although the criteria for the clinical diagnosis of drug abuse and dependence has been and will continue to be modified based on scientific research, the behavioral sequelae associated with addiction revolve around a heightened response to rewarding stimuli and the uncontrollable behavior that individuals present in order to consume the rewarding stimuli. Various models of addiction suggest several stages and processes that contribute to addiction (discussed in Chapter 3). However, they all begin with the initial hedonic or pleasurable response to substances that lends itself to increased motivation to acquire and consume substances, as well as impulsivity and loss of control over their use. Tolerance and withdrawal are also vital processes that contribute to the maintenance of substance use despite a desire to quit.

What makes addiction so complex is the multidimensional processes that lead to a cascade of neural and biological events. These events increase the risk for other illnesses such as AIDS, cancer, and cardiovascular and respiratory diseases, as well as mental disorders including psychosis. Use of substances can also transmit harmful effects to unborn fetuses such as in the case of fetal alcohol syndrome, premature birth and neonatal abstinence syndrome. Individuals with addiction are also at risk for failing to meet their responsibilities. For example, substance abuse increases the risk for dropping out of school (27% of high-school dropouts smoked cannabis, 10% abused prescription drugs, 42% consumed alcohol; US Substance Abuse and Mental Health Administration, www.samhsa.gov/data), one in six unemployed individuals use substances (www.samhsa.gov/data) and ~70% of incarcerated offenders regularly used drugs prior to their incarceration (US Dept. of Justice Report, www.bjs.gov/content/dcf/duc.cfm).

Most of these consequences persist despite discontinuation from drug use. Thus, prevention and treatment strategies should focus on modifying behaviors that promote protracted abstinence. Current research in SUD intervention is focusing on more targeted treatment, given that current programs have very poor success rates, with ~70% relapse within the first year.

The Demography of Addiction

Epidemiological studies make sense of connections between demographic factors and substance use. These studies demonstrate associations between certain demographics and prevalence of substance use. For instance, stimulant users in developed countries have been found to be typically lower-class, 20–25-year-old males (Babor, 1994). US national survey data also show that alcohol use varies by age, sex and ethnic background. For instance, young males tend to drink alcohol more than females and older individuals. Similar associations are also found in nicotine use such that higher rates of smoking are found in those of lower social class (Jarvis *et al.*, 2008). Dynamic factors, however, change the trends in substance users. For example, while opioid use was historically most prevalent in urban 18–25-year-old males in the USA, there has been a shift toward more widespread use that includes a greater number of female users in the last few years (Cicero *et al.*, 2014). There are also commonalities in the demographic characteristics of users across different substances. In general, substance-abusing individuals tend to be male, young and have low socioeconomic status. Notably, accessibility of substances also plays a large role in these associations, contributing to alcohol and nicotine use being the most prevalent of all substance use. However, of all of these characteristics, age appears to be the most important demographic correlate.

Several factors contribute to the abuse potential within certain demographic populations. Interactions of the drug with other disorders can influence its likelihood for abuse and dependence. For instance, populations characterized as being high in risk-taking behavior are more likely to abuse substances. Psychiatric disorders that are associated with an increased risk of abuse include schizophrenia, bipolar disorder, depression and attention deficit/hyperactivity disorder (ADHD). Genetic factors also play an important role in the risk for addiction. Implicated genes are typically those that regulate dopaminergic functioning, such as the dopamine receptor D4 gene (Filbey *et al.*, 2008).

The Stigma of Addiction

Historically, addiction has been and, to some extent, continues to be viewed as a "disorder of free will." Such perception implies that addiction is a social issue that should be handled by social solutions. These putative social issues include failings in childhood upbringing including the home and school environment, aversive conditions including neglect

and abuse, cultural acceptance, absence of positive influences and role models, unstructured environments, and negative peer and societal influences. While some of these social factors may contribute toward the initiation of substance use, growing empirical evidence does not support social issues as the core basis of addiction. Let us take the example of alcohol. The large majority of the population consumes alcohol on a regular basis (52% of American adults are current regular drinkers); however, only 10% of the drinking population develops an addiction (Blackwell *et al.*, 2014). This demonstrates that there is more to the equation than "free will."

Social solutions have also largely failed to remediate those who are addicted, primarily because they do not address the underlying etiology. Because of the stigma of addiction, those with addiction: 1) do not seek the necessary treatment; 2) do not receive the necessary social support; or 3) receive largely ineffective treatment that does not address the underlying mechanisms of addiction.

The Diagnosis of Addiction

The clinical diagnoses of mental health disorders rely on classification systems that have been developed over centuries. These classification systems differ based on their purpose for classification (clinical, research or administrative objectives), as well as emphasis on discerning features of diagnostic categories (phenomenology versus etiology). The two most prominent systems are the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) and the *International Classification of Diseases* (ICD). The ICD, developed by the World Health Organization, published the first section for mental health disorders in 1949 within its 6th edition. Based on this, the American Psychiatric Association Committee on Nomenclature and Statistics developed the 1st edition of the DSM in 1952. The DSM then became the first official manual of mental disorders to focus on clinical use. The DSM-5, which was published in 2013 and implemented in 2014, is the most recent version.

In terms of the diagnosis of addiction, the DSM-5 classifies the diagnosis of SUDs based on evidence of impaired control, social impairment, risky use and pharmacological criteria. The major modification from DSM-IV to DSM-5 is the combination of the categorical symptoms in DSM-IV into a continuum in DSM-5 (Table 1.2). Thus, rather than dimorphic diagnoses of substance abuse and dependence, a unidimensional diagnosis of SUD is evaluated on a scale from mild to severe depending on the number of symptoms presented. This decision was

Table 1.2 Modifications to addiction diagnosis from DSM-IV to DSM-5.

Criterion	DSM-IV substance abuse	DSM-IV substance dependence	DSM-5 SUD
Tolerance		X	X
Withdrawal		X	X
Taken more/longer than intended		X	X
Desire/unsuccessful efforts to quit use		X	X
Great deal of time taken by activities involved with use		X	X
Use despite knowledge of problems associated with use		X	X
Important activities given up because of use		X	X
Recurrent use resulting in a failure to fulfill important role obligations	X		X
Recurrent use resulting in physically hazardous behavior (e.g. driving)	X		X
Continued use despite recurrent social problems associated with use	X		X
Craving for the substance			X

based on evidence showing that symptoms of abuse and dependence were not independent of each other and formed a single dimension. As a result, two to three symptoms would classify as "mild SUD", four to five symptoms as "moderate SUD" and six to eleven symptoms as "severe SUD." Since the inception of this new classification system for addiction diagnosis, opponents of this system have argued that the unidimensional classification does not reflect the discrete nature of the features of addiction, namely, withdrawal, tolerance and craving. Indeed, these constructs have been viewed as conceptually and empirically distinct, and subsequent chapters will discuss the neuroscientific foundations of each of these constructs.

Another modification is the overarching criteria for SUDs independent of substance, as well as the inclusion of behavioral addictions (e.g. gambling disorder). Incidentally, DSM-5 includes a section with tools to

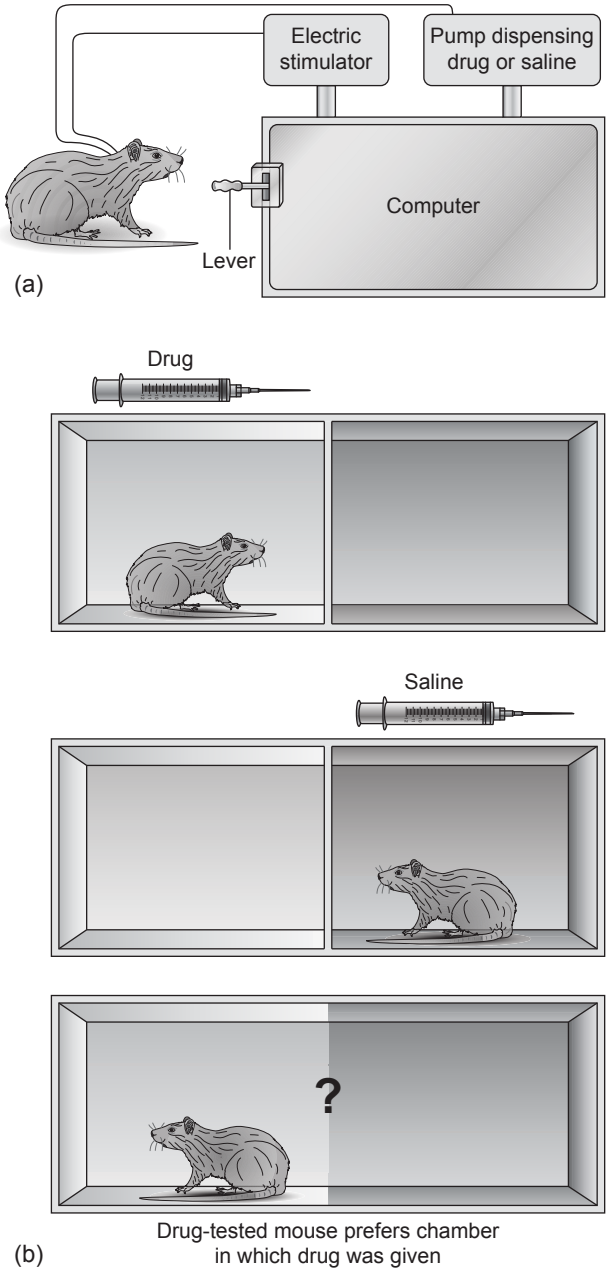

Figure 1.2 Animal behavioral paradigms in addiction studies. (a) In self-administration models, animals continuously perform an action (e.g. pressing a lever) in order to receive a

improve the diagnosis of personality disorders, and incorporates diagnoses that may be considered for future iterations of the DSM. This section (section III) includes internet gaming disorder and caffeine use disorder.

A Brain Disease Model of Addiction

As mentioned earlier, the view that addiction is a social issue overlooks the role of the brain in the behavioral symptoms related to addiction. By doing so, interventions attempt to modify behavior that may not be directly related to the underlying mechanisms. What are these underlying mechanisms of addiction? Much of what we know about addiction as a brain disease originates from seminal animal research that began ~30 years ago. For instance, animal experiments utilizing intracranial self-stimulation demonstrated how animals will readily self-administer drugs of abuse and how these drugs alter the animal's reward threshold (Figure 1.2a). In a classic study of the positive reinforcing effects of morphine, Weeks and colleagues trained rats to self-deliver morphine intravenously (Weeks, 1962). They discovered that the unrestrained rats self-injected morphine and that the greater the dose, the less they self-injected. Classical conditioning models, such as conditioned place preference, show the development of paired associations between the rewarding properties of drugs and the cue that signals exposure to the drug, suggesting adaptations in reward learning mechanisms (Figure 1.2b). Behavior sensitization models assess the result of repeated drug exposure and suggest an augmented response following continued use. These models demonstrate the progression of addiction from the initial hedonic response to the drug ("liking" the drug) to that of yearning or craving ("wanting" the drug). For example, behavior sensitization has been described in terms of locomotor activity in rats sensitized to higher doses of amphetamine (e.g. 2.0 mg/kg intraperitoneally) where an initial slowing is later followed by an increase (Leith & Kuczenski, 1982). Another example is the reinstatement model, which also assesses how repeated drug exposure impacts behavior but is used to test

reward or receive intracranial current in brain-rewarding loci (self-stimulation). (b) In place-preference models, animals spend more time in an environment where they had repeatedly received a drug, demonstrating positive reinforcing mechanisms of drugs.
(From Camí & Farré, 2003. © 2003 Massachusetts Medical Society, USA.)

mechanisms of drug relapse. In these models, an established operant response for the drug such as lever pressing that has been extinguished re-emerges or reinstates. For example, place preference to previously drug-paired environments can be reinstated following extinction in animals. These animal models have been translated into human models (discussed in Chapter 2), and with advanced technologies (discussed in Chapter 2) and focused scientific research, there is now a growing understanding of the key role of neurobiological mechanisms underlying processes related to addiction. These processes are discussed individually in subsequent chapters.

The initial effects of substances on behavior widely vary because each drug's mechanism of action on the brain is unique. Opioids bind to μ receptors in the brain, which results in feelings of euphoria, sedation and tranquility. The importance of μ receptors is demonstrated in studies where mice lacking this receptor do not exhibit these behavioral effects, and also do not become physically addicted. Cannabis also causes relaxation but exerts its effects by binding to cannabinoid (CB1) receptors in the brain. The effects of cannabis also include a sense of well-being, as well as slowing of cognitive functions. Slowing of cognitive functions also results from alcohol, although alcohol modulates activity in several receptors including serotonin (5-hydroxytryptamine, 5-HT), nicotinic, γ-aminobutyric acid (GABA) and *N*-methyl-D-aspartate (NMDA) receptors. Unlike depressants, such as alcohol, psychostimulants, in general, result in opposite effects such as increased alertness, arousal, concentration and motor activity by blocking the reuptake of dopamine, norepinephrine and serotonin. This results in a rapid release and accumulation of neurotransmitters in the synaptic cleft.

However, despite this wide range of mechanisms and effects, virtually all addictive substances target brain regions in the medial portion of the limbic and frontal lobes. These regions form a neural pathway that is innervated primarily by dopaminergic projections that originate from the ventral tegmental area (VTA) in the midbrain and project to the amygdala and the nucleus accumbens. Because of dopamine's role in the hedonic response, this neural pathway is referred to as the dopaminergic reward pathway due to its role in processing rewarding drug and non-drug stimuli (illustrated in Figure 1.3). In addition to dopamine, this pathway is also modulated by opioids, GABA and endocannabinoids, and also processes emotion and motivation. This pathway is, therefore, important in the conscious experience of taking a drug, drug craving and compulsion. It is within this pathway that substances exert their effects. Thus, brain regions within this pathway are likely to endure pervasive