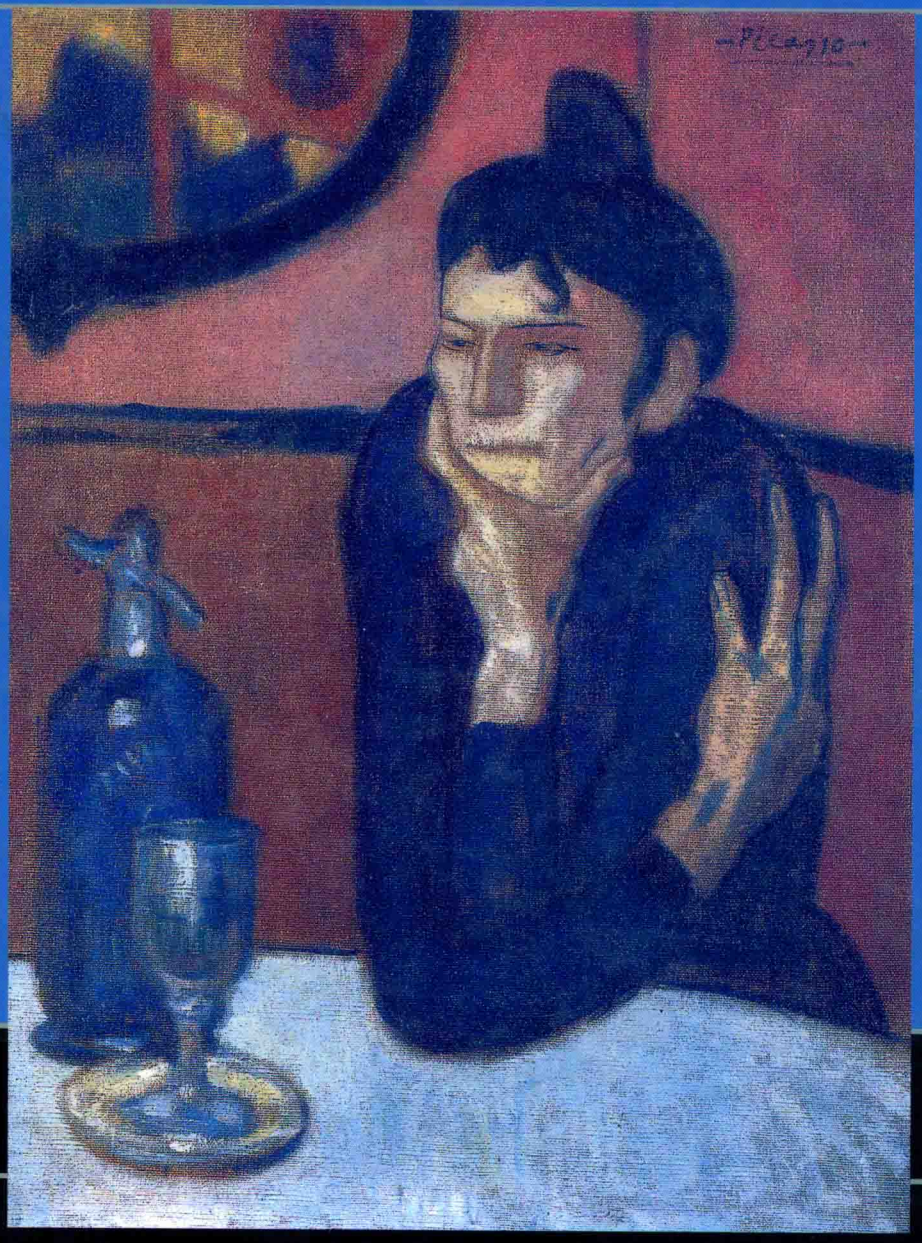
Neurobiology of Addiction



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NEUROBIOLOGY OF ADDICTION

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NEUROBIOLOGY OF ADDICTION

"Drugs don't affect me"
Dr. Theodora J Koob

Preface

This book began with an idealistic goal to summarize, integrate, and synthesize the world's literature on the Neurobiology of Addiction under one conceptual framework, in one volume. As we embarked on this journey, it became increasingly evident that this was a Herculean task that required an enormous commitment to find original sources, review diverse topics, search under conceptual stones, and select relevant facts, papers and frameworks, and ultimately limit our appetite for citing every paper.

The journey took over two years and led to the uncovering of heretofore unknown intellectual gems (to us anyway) and some contradictions—but also a surprising number of neurobiological consistencies and commonalities across the spectrum of addictive drugs. What evolved was, what we think, is a reasonably objective view of the field, with a concerted attempt to accomplish what we set out to do.

As a result, there is a chapter on *What is Addiction?* and another on *Animal Models of Addiction* to guide the reader through the conceptual and technical framework of the book. What follows are five chapters on the major classes of drugs of addiction: *Psychostimulants, Opioids, Alcohol, Nicotine, and Cannabinoids*. Each chapter stands on its own and integrates human use and addiction patterns and behavioral mechanisms with the neurobiology explored at three levels: neurocircuitry (neuropharmacology), cellular (electrophysiology), and molecular (molecular measures and molecular genetic approaches). Appendices 1–5 provide human case histories and anecdotes describing addiction profiles and personal experiences relevant to each drug chapter.

These levels of analysis are arbitrary and overlap but provide a succinct framework for integration across disciplines. Human neuroimaging has been incorporated as a separate chapter to allow a view of common elements in the imaging field and to reduce redundancy of technique, approach, and methodology.

Towards the end of the book, there is a chapter on *Neurobiological Theories of Addiction* which explores the different conceptual views of prominent investigators in the field, from both a neurobiological and evolving historical perspective. An attempt is made to integrate the different theories into a heuristic model to account for most of the stages of the addiction cycle. The last chapter, *Drug Addiction: Transition from Neuroadaptation to Pathophysiology*, is what we unabashedly admit is our world view of the neurobiology of addiction; as such, this final chapter may be considered parochial. Nevertheless, we believe, that after two years of intense research, we can bring a unique view to the field, as if we were in a zeppelin floating above the vast sea of data.

Several facts are worth noting. First, an attempt was made to trace every single statement to its original source, and not to use secondary references. If, perchance, we have failed, we welcome corrections. Second, we made a valiant attempt to fully cover the field. If we have left out an important component of a given piece of the field, we also welcome input. Third, we restricted our journey to the major drugs of addiction and left out numerous other drugs of abuse and drugs of dependence (with a little "d"; see Chapter 1). We did not cover psychedelics, inhalants, steroids, caffeine, benzodiazepines, gambling, etc. Such a broadened perspective will be saved for another day.

George F Koob

Michel Le Moal

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This book would not have been possible without the following contributions. First and foremost, without the tireless efforts of Michael A. Arends, we would still be writing. Mike found and tracked down references (sometimes literally hundreds of years old) from the world over, coordinated all tables, figures, figure legends, and references, and leant his incredibly thorough editing skill.

All figures for the book were redrawn from their original sources by Janet Hightower of The Scripps Research Institute Biomedical Graphics department.

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Contents

7. Cannabinoids

8. Imaging

9. Neurobiological Theories of Addiction

10. Drug Addiction: Transition from Neuroadaptation to Pathophysiology

CHAPTER

1

What is Addiction?

OUTLINE

DEFINITIONS OF ADDICTION

Drug Use, Drug Abuse, and Drug Addiction

Drug addiction, also known as Substance Dependence (American Psychiatric Association, 1994), is a chronically relapsing disorder that is characterized by (1) compulsion to seek and take the drug, (2) loss of control in limiting intake, and (3) emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented (defined here as dependence) (Koob and Le Moal, 1997). The occasional but limited use of an abusable drug clinically is distinct from escalated drug use, loss of control over limiting drug intake, and the emergence of chronic compulsive drug-seeking that characterizes addiction. Modern views have focused on three types of drug use: (1) occasional, controlled or social use, (2) drug abuse or harmful use, and (3) drug addiction. An important goal of current neurobiological research on addiction is to understand the neuropharmacological and neuroadaptive mechanisms within specific neurocircuits that mediate the transition between occasional, controlled drug use and the loss of behavioral control over drug-seeking and drug-taking that defines chronic addiction (Koob and Le Moal, 1997).

The critical nature of the distinction between drug use, abuse and dependence has been illuminated by data showing that approximately 15.6 per cent (29 million) of the U.S. adult population will go on to engage in nonmedical or illicit drug use at some time in their lives, with approximately 3.1 per cent (5.8 million) of the U.S. adult population going on to drug abuse and 2.9 per cent (5.4 million) going on to Substance Dependence on illicit drugs (Grant and Dawson, 1998; Grant *et al.*, 2005). For alcohol, 51 per cent (120 million) of people over the age of 12 were current users, 23 per cent (54 million) engaged in binge drinking, and 7 per cent (16 million) were defined as heavy drinkers. Of these current users, 7.7 per cent (18 million) met the criteria for Substance Abuse or Dependence on Alcohol (see *Alcohol* chapter). For tobacco, 30 per cent (71.5 million) of people aged 12 and older reported past-month use of a tobacco product. Also, 19 per cent (45 million) of persons in the U.S. smoked every day in the past month. From the 1992 National Comorbidity Survey, 75.6 per cent of 15–54-year-olds ever used tobacco, with 24.1 per cent

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TABLE 1.1 Estimated Prevalence Among 15–54-Year-Olds of Nonmedical Use and Dependence Among Users (1990–1992) from The National Comorbidity Survey

	Ever used (%)	Prevalence of dependence (%)	Dependence among users (%)
Tobacco	75.6	24.1	31.9
Alcohol	91.5	14.1	15.4
Illicit Drugs	51.0	7.5	14.7
Cannabis	46.3	4.2	9.1
Cocaine	16.2	2.7	16.7
Stimulants	15.3	1.7	11.2
Anxiolytics	12.7	1.2	9.2
Analgesics	9.7	0.7	7.5
Psychedelics	10.6	0.5	4.9
Heroin	1.5	0.4	23.1
Inhalants	6.8	0.3	3.7

[Reproduced with permission from Anthony *et al.*, 1994.]

meeting the criteria for Dependence (Anthony *et al.*, 1994) (see *Nicotine* chapter).

The number of individuals meeting the criteria for Substance Dependence on a given drug as a function of ever having used the drug varies between drugs. According to data from the 1990–1992 National Comorbidity Survey, the percentage addicted to a given drug, of those people who ever used the drug, decreased in the following order: *tobacco > heroin > cocaine > alcohol > marijuana* (Anthony *et al.*, 1994) (**Table 1.1**). More recent data derived from the National Household Survey on Drug Abuse (Substance Abuse and Mental Health Services Administration, 2003) showed that the percentage addicted to a given drug, of those who ever used, decreases in the following order: *heroin > cocaine > marijuana > alcohol* (**Fig. 1.1**). These more recent data suggest unsettling evidence of an overall trend for a significant increase in Substance Dependence with marijuana (see *Cannabinoids* chapter).

The cost to society of drug abuse and drug addiction is prodigious in terms of both direct costs and indirect costs associated with secondary medical events, social problems, and loss of productivity. In the United States alone, it is estimated that illicit drug abuse and addiction cost society $161 billion (Office of National Drug Control Policy, 2001; see also Uhl and Grow, 2004). It is estimated that alcoholism costs society $180 billion per year (Yi *et al.*, 2000), and tobacco addiction $155 billion (Centers for Disease Control and Prevention, 2004). In France, the total cost of drug use is USD 41 billion (including $22 billion for alcohol, $16 billion for tobacco, and nearly $3 billion for illicit drugs) (Kopp and Fenoglio, 2000).

Addiction and *Substance Dependence* will be used interchangeably throughout this text and will refer to a final stage of a usage process that moves from drug use to abuse to addiction. Drug addiction is a disease and, more precisely, a *chronic* disease (Meyer, 1996). As such, it can be defined by its diagnosis, etiology, and pathophysiology as a chronic relapsing disorder (**Fig. 1.2**). The associated medical, social, and occupational difficulties that usually develop during the course of addiction do not disappear after detoxification. Addictive drugs are hypothesized to produce changes in brain pathways that endure long after the person stops taking them. These protracted brain changes and the associated personal and social difficulties put the former patient at risk of relapse (O'Brien and McLellan, 1996), a risk higher than 60 per cent within the year that follows discharge (Finney and Moos, 1992; Hubbard *et al.*, 1997;

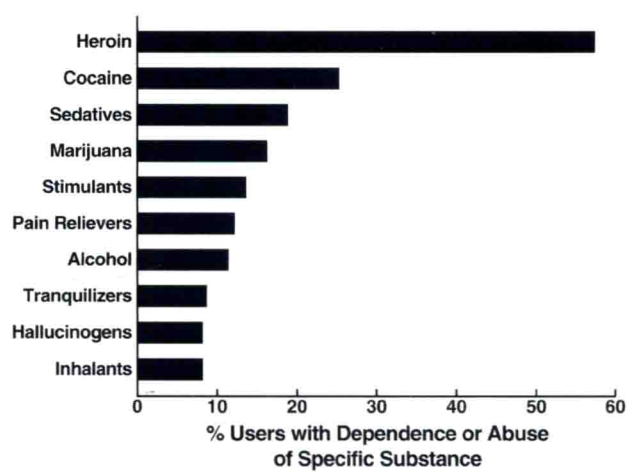

FIGURE 1.1 Dependence or abuse of specific substances among past-year users of substance (Substance Abuse and Mental Health Services Administration, 2003). Heroin: 57.4% (0.2 million), Cocaine: 25.6% (1.5 million), Marijuana: 16.6% (4.2 million).

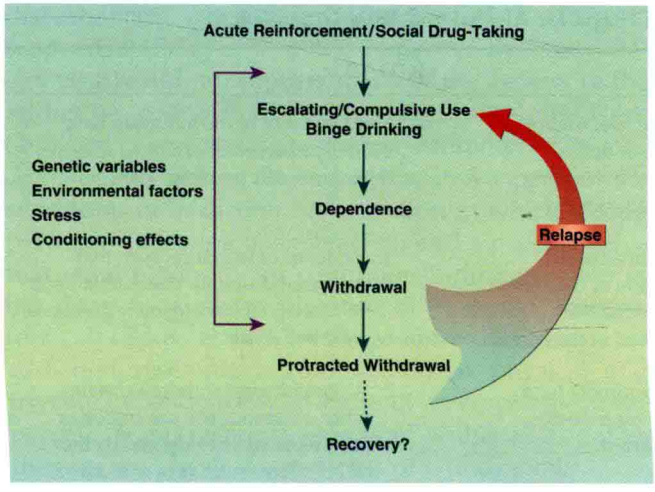

FIGURE 1.2 Stages of addiction to drugs of abuse. Drug-taking invariably begins with social drug-taking and acute reinforcement and often, but not exclusively, then moves in a pattern of use from escalating compulsive use to dependence, withdrawal, and protracted abstinence. During withdrawal and protracted abstinence, relapse to compulsive use is likely to occur with a repeat of the cycle. Genetic factors, environmental factors, stress, and conditioning all contribute to the vulnerability to enter the cycle of abuse/dependence and relapse within the cycle.

McLellan and McKay, 1998; McLellan *et al.*, 2000). While much of the initial study of the neurobiology of drug addiction focused on the acute impact of drugs of abuse (analogous to comparing no drug use to drug use), the focus is now shifting to chronic administration and the acute and long-term neuroadaptive changes in the brain that result in relapse. Cogent arguments have been made which support the hypothesis that addictions are similar in their chronic relapsing properties and treatment efficacy to other chronic relapsing disorders such as diabetes, asthma, and hypertension (McLellan *et al.*, 2000). The purpose of current neuroscientific drug abuse research is to understand the cellular and molecular mechanisms that mediate the transition from occasional, controlled drug use to the loss of behavioral control over drug-seeking and drug-taking that defines chronic addiction (Koob and Le Moal, 1997).

Diagnostic Criteria of Addiction

The diagnostic criteria for addiction as described by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association, 1994), also have evolved over the past 30 years with a shift from the emphasis and necessary criteria of tolerance and withdrawal to other criteria directed more at compulsive use. In the DSM-IV, tolerance and withdrawal form two of seven potential criteria. The criteria for Substance Dependence outlined in the DSM-IV closely resemble those outlined by the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) (World Health Organization, 1992) (**Tables 1.2** and **1.3**). The number of criteria met by drug addicts vary with the severity of the addiction, the stage of the addiction process, and the drug in question (Chung and Martin, 2001). For example, in adolescents, the most frequently observed criteria are *much time getting or recovering from use* (DSM-IV criteria #5 and #7), *continued use despite problems in social and occupational functioning* (DSM-IV criterion #6), and *tolerance or withdrawal* (DSM-IV criteria #1 and #2) (Crowley *et al.*, 1998) (see *Cannabinoids* chapter).

TABLE 1.2 DSM-IV and ICD-10 Diagnostic Criteria for *Alcohol and Drug Abuse/Harmful Use*

DSM-IV **Alcohol and drug abuse**	ICD-10 **Harmful use of alcohol and drugs**
A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following occurring within a 12-month period: 1. recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home. 2. recurrent substance use in situations in which use is physically hazardous. 3. recurrent substance-related legal problems. 4. continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the drug. B. The symptoms have never met the criteria for substance dependence for the same class of substance.	A. A pattern of substance use that is causing damage to health. The damage may be physical or mental. The diagnosis requires that actual damage should have been caused to the mental or physical health of the user. B. No concurrent diagnosis of the substance dependence syndrome for same class of substance.

TABLE 1.3 DSM-IV and ICD-10 Diagnostic Criteria for *Alcohol and Drug Dependence*

	DSM-IV	ICD-10
Clustering criterion	A. A maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by three or more of the following occurring at any time in the same 12-month period:	A. Three or more of the following have been experienced or exhibited at some time during the previous year:
Tolerance	1. Need for markedly increased amounts of a substance to achieve intoxication or desired effect; or markedly diminished effect with continued use of the same amount of the substance.	1. Evidence of tolerance, such that increased doses are required in order to achieve effects originally produced by lower doses.
Withdrawal	2. The characteristic withdrawal syndrome for a substance or use of a substance (or a closely related substance) to relieve or avoid withdrawal symptoms.	2. A physiological withdrawal state when substance use has ceased or been reduced as evidenced by the characteristic substance withdrawal syndrome, or use of substance (or a closely related substance) to relieve or avoid withdrawal symptoms.
Impaired control	3. Persistent desire or one or more unsuccessful efforts to cut down or control substance use.	3. Difficulties in controlling substance use in terms of onset, termination, or levels of use.
	4. Substance used in larger amounts or over a longer period than the person intended.	
Neglect of activities	5. Important social, occupational, or recreational activities given up or reduced because of substance use.	4. Progressive neglect of alternative pleasures or interests in favor of substance use; or
Time spent	6. A great deal of time spent in activities necessary to obtain, to use, or to recover from the effects of substance used.	A great deal of time spent in activities necessary to obtain, to use, or to recover from the effects of substance use.
Inability to fulfil roles	None	None
Hazardous use	None	None
Continued use despite problems	7. Continued substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by use.	5. Continued substance use despite clear evidence of overtly harmful physical or psychological consequences.
Compulsive use	None	6. A strong desire or sense of compulsion to use substance.
Duration criterion	B. No duration criterion separately specified. However, several dependence criteria must occur repeatedly as specified by duration qualifiers associated with criteria (e.g., 'often', 'persistent', 'continued').	B. No duration criterion separately specified.
Criterion for subtyping dependence	*With physiological dependence:* Evidence of tolerance or withdrawal (i.e., any of items A-1 or A-2 above are present). *Without physiological dependence:* No evidence of tolerance or withdrawal (i.e., none of items A-1 or A-2 above are present).	None

Dependence View of Addiction

Historically, definitions of addiction began with definitions of dependence. Himmelsbach defined physical dependence as:

> '... an arbitrary term used to denote the presence of an acquired abnormal state wherein the regular administration of adequate amounts of a drug has, through previous prolonged use, become requisite to physiologic equilibrium. Since it is not yet possible to diagnose physical dependence objectively without withholding drugs, the *sine qua non* of physical dependence remains the demonstration of a characteristic abstinence syndrome' (Himmelsbach, 1943).

Eventually this definition evolved into the definition for physical dependence or 'intense physical

disturbances when administration of a drug is suspended' (Eddy *et al.*, 1965). However, this terminology clearly did not capture many of the aspects of the addictive process where no *physical* signs were observed, necessitating a second definition of *psychic dependence* to capture the more *behavioral* aspects of the symptoms of addiction: 'A condition in which a drug produces "a feeling of satisfaction and a psychic drive that require periodic or continuous administration of the drug to produce pleasure or to avoid discomfort"...' (Eddy *et al.*, 1965). Modern definitions of addiction resemble a combination of physical and psychic dependence with more of an emphasis on the psychic or motivational aspects of withdrawal, rather than on the physical symptoms of withdrawal:

> '*Addiction* from the Latin verb "addicere", to give or bind a person to one thing or another. Generally used in the drug field to refer to chronic, compulsive, or uncontrollable drug use, to the extent that a person (referred to as an "addict") cannot or will not stop the use of some drugs. It usually implies a strong (Psychological) Dependence and (Physical) Dependence resulting in a Withdrawal Syndrome when use of the drug is stopped. Many definitions place primary stress on psychological factors, such as loss of self-control and over powering desires; i.e., addiction is any state in which one craves the use of a drug and uses it frequently. Others use the term as a synonym for physiological dependence; still others see it as a combination (of the two)' (Nelson *et al.*, 1982).

Unfortunately, the word *dependence* has multiple meanings. Any drug can produce dependence if dependence is defined as the manifestation of a withdrawal syndrome upon cessation of drug use, but meeting the DSM-IV criteria for *Substance Dependence* is much more than a manifestation of a withdrawal syndrome, but rather is equivalent to addiction. For the purposes of this book, *dependence* with a lower-case 'little d' will refer to the manifestation of a withdrawal syndrome, whereas *Dependence* with a capital 'big D' will refer to Substance Dependence as defined by the DSM-IV or addiction. The words *Substance Dependence* (as defined by the DSM-IV), *addiction* and *alcoholism* will be held equivalent for this book.

Psychiatric View of Addiction

From a psychiatric perspective, drug addiction has aspects of both impulse control disorders and compulsive disorders. Impulse control disorders are characterized by an increasing sense of tension or arousal before committing an impulsive act—pleasure, gratification or relief at the time of committing the act—and there may or may not be regret, self-reproach or guilt following the act (American Psychiatric Association, 1994). In contrast, compulsive disorders are characterized by anxiety and stress before committing a compulsive repetitive behavior and relief from the stress by performing the compulsive behavior. As an individual moves from an impulsive disorder to a compulsive disorder, there is a shift from positive reinforcement driving the motivated behavior to negative reinforcement driving the motivated behavior (Koob, 2004) (**Fig. 1.3**). Drug addiction has been conceptualized as a disorder that progresses from impulsivity to compulsivity in a collapsed cycle of addiction comprised of three stages: preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect. Different theoretical perspectives ranging from experimental psychology, social psychology, and neurobiology can be superimposed on these three stages which are conceptualized as feeding into each other, becoming more intense, and ultimately leading to the pathological state known as addiction (Koob and Le Moal, 1997) (**Fig. 1.4**).

Psychodynamic View of Addiction

A psychodynamic view of addiction that integrates well with the neurobiology of addiction is that of Khantzian and colleagues (Khantzian, 1985, 1990, 1997) with a focus on the factors leading to vulnerability for addiction. This perspective is deeply rooted in clinical practice and in psychodynamic concepts developed in a contemporary perspective in relation to substance use disorders. The focus of this approach is on developmental difficulties, emotional disturbances, structural (ego) factors, personality organization, and the building of the self. It is important to note that this contemporary perspective contrasts with a classic but not abundant psychoanalytic literature on the subject which emphasizes the pleasurable aspects of drugs and the regressive aspects of drug use.

Two critical elements (disordered emotions and disordered self-care) and two contributory elements (disordered self-esteem and disordered relationships) have been identified, which have evolved into a modern self-medication hypothesis, where individuals with substance use disorders are hypothesized to take drugs as a 'means to cope with painful and threatening emotions.' In this conceptualization, addicted individuals experience states of subjective distress and suffering that may or may not be associated with conditions meeting DSM-IV criteria for a psychiatric diagnosis (American Psychiatric Association, 1994).

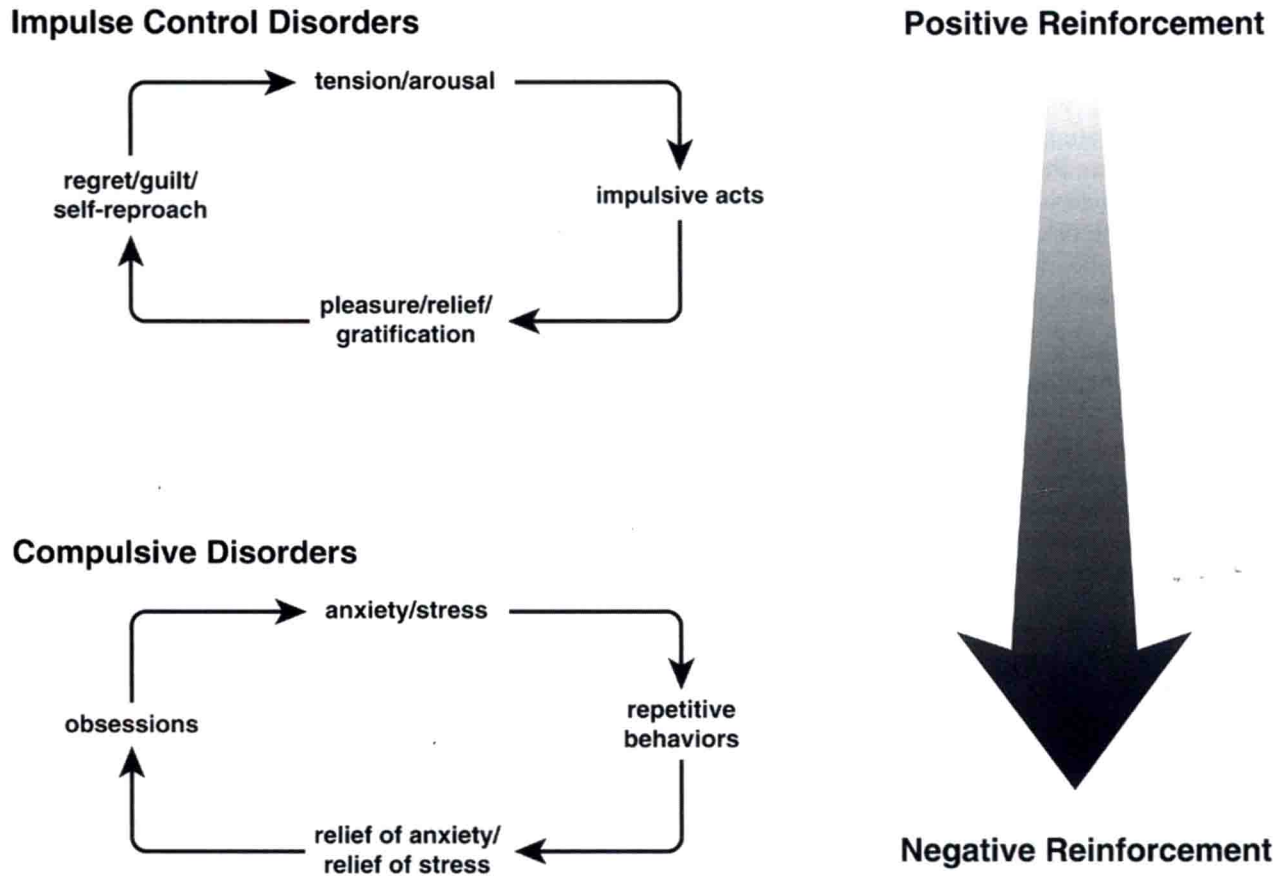

FIGURE 1.3 Diagram showing stages of impulse control disorder and compulsive disorder cycles related to the sources of reinforcement. In impulse control disorders increasing tension and arousal occur before the impulsive act, with pleasure, gratification, or relief during the act. Following the act there may or may not be regret or guilt. In compulsive disorders, there are recurrent and persistent thoughts (obsessions) that cause marked anxiety and stress followed by repetitive behaviors (compulsions) that are aimed at preventing or reducing distress (American Psychiatric Association, 1994). Positive reinforcement (pleasure/gratification) is more closely associated with impulse control disorders. Negative reinforcement (relief of anxiety or relief of stress) is more closely associated with compulsive disorders. [Reproduced with permission from Koob, 2004.]

Addicts have feelings that are overwhelming and unbearable and may consist of an affective life that is absent and nameless. From this perspective, drug addiction is viewed as an attempt to medicate such a dysregulated affective state. The suffering of the patient is deep-rooted in disordered emotions characterized at their extremes either by unbearable painful affect or by a painful sense of emptiness. Others cannot express personal feelings or cannot access emotions and are hypothesized to suffer from alexithymia, defined as 'a marked difficulty to use appropriate language to express and describe feelings and to differentiate them from bodily sensation' (Sifneos, 2000).

Such self-medication may be drug-specific in that patients may have a preferential use of drugs that fits with the nature of the painful affective states that they are self-medicating. Opiates might be effective in reducing psychopathological states of violent anger and rageful feelings. Others suffering from anhedonia, anergia, or lack of feelings, will prefer the activating properties of psychostimulants. Some flooded in their feelings, or cut off from feelings, will welcome repeated moderate doses of alcohol or depressants as medicine to express feelings that they are not able to communicate. Thus, in some cases, the subjects operate to relieve painful feelings, in others, the operative motive is to control or express feelings (Khantzian, 1995, 1997; Khantzian and Wilson, 1993). The common element to this hypothesis is that each class of drugs serves as an antidote to dysphoric states and acts as a 'replacement for a defect in the psychological structure' of such individuals (Kohut, 1971). The paradox is that the choice of drugs to self-medicate such emotional pain will later by itself perpetuate it, thereby continuing a life revolving around drugs.

Disordered self-care is hypothesized to combine with a disordered emotional life to become a principal

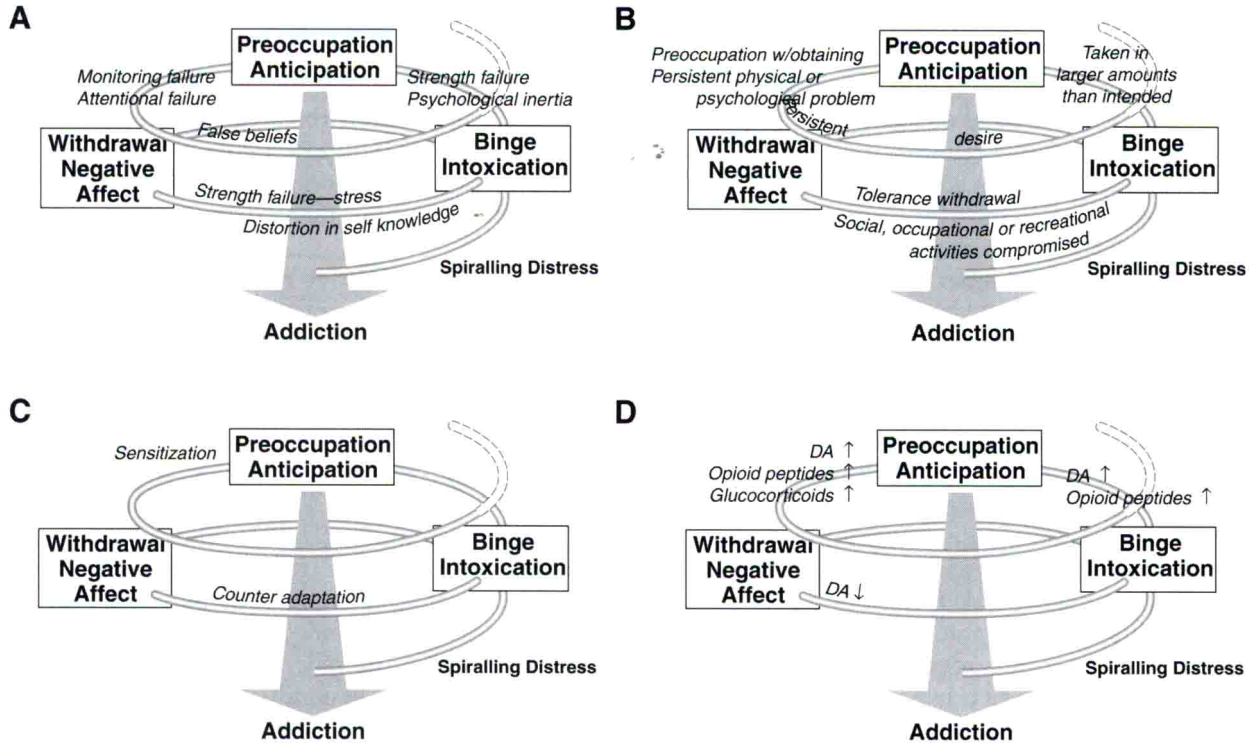

FIGURE 1.4 Diagram describing the spiraling distress—addiction cycle from four conceptual perspectives: social psychological, psychiatric, dysadaptational, and neurobiological. Note that the addiction cycle is conceptualized as a spiral that increases in amplitude with repeated experience, ultimately resulting in the pathological state known as addiction. **(A)** The three major components of the addiction cycle—preoccupation/anticipation, binge/intoxication, and withdrawal/negative affect—and some of the sources of potential self-regulation failure in the form of underregulation and misregulation. **(B)** The same three major components of the addiction cycle with the different criteria for substance dependence incorporated from the DSM-IV. **(C)** The places of emphasis for the theoretical constructs of sensitization and counteradaptation. **(D)** The hypothetical role of different neurochemical and endocrine systems in the addiction cycle. Small arrows refer to increased functional activity. DA, dopamine; CRF, corticotropin-releasing factor. [Reproduced with permission from Koob and Le Moal, 1997.]

determinant of substance use disorders. Self-care deficits reflect an inability to ensure one's self-preservation and are characterized by an inability to anticipate or avoid harmful and dangerous situations, and an inability to use appropriate judgment and feeling as guides in the face of danger. Thus, self-care deficits reflect an inability to appropriately experience emotions and appreciate the consequences of dangerous behaviors, and the core element of this psychodynamic perspective is a dysregulated emotional system or systems in individuals vulnerable to addiction.

This psychodynamic approach integrates well with a growing amount of evidence for a critical role of dysregulated brain reward and stress systems, from studies on the neurobiology of addiction using animal models that have developed from a physiological framework (see chapters that follow). However, from a neurobiological perspective, there is the additional insult to the personality produced by the direct effects of the drugs themselves to perpetuate, and actually *create*, such character flaws (Koob, 2003).

Social Psychological / Self-regulation View of Addiction

At the social psychology level, self-regulation failure has been argued as the root of the major social pathology in present times (Baumeister *et al.*, 1994). From this perspective there are important self-regulation elements that may be involved in the different stages of addiction to drugs, as well as in other pathological behaviors such as compulsive gambling and binge eating (Baumeister *et al.*, 1994). Such self-regulation failures ultimately may lead to addiction in the case of drug use or an addiction-like pattern with nondrug behaviors. Underregulation as reflected in strength deficits, failure to establish standards or conflicts in standards, and attentional failures as well as misregulation (misdirected attempts to self-regulate) can contribute to the development of addiction-like patterns of behavior (**Fig. 1.4**). The transition to addiction can be facilitated by lapse-activated causal patterns. That is, patterns of behavior that contribute to the transition from an

initial lapse in self-regulation to a large-scale breakdown in self-regulation can lead to spiraling distress (Baumeister *et al.*, 1994). In some cases, the first self-regulation failure can lead to emotional distress which sets up a cycle of repeated failures to self-regulate and where each violation brings additional negative affect, resulting in spiraling distress (Baumeister *et al.*, 1994). For example, a failure of strength may lead to initial drug use or relapse, and other self-regulation failures can be recruited to produce an entrance to, or prevent an exit from, the addiction cycle.

At a neurobehavioral level, such dysregulation again may be reflected in deficits of information-processing, attention, planning, reasoning, self-monitoring, inhibition, and self-regulation, many of which involve functioning of the frontal lobe (Giancola *et al.*, 1996a,b) (see chapters that follow). Executive function deficits, self-regulation problems, and frontal lobe dysfunctions or pathologies constitute a risk factor for biobehavioral disorders including drug abuse (Dawes *et al.*, 1997). Deficits in frontal cortex regulation in children or young adolescents predict later drug and alcohol consumption, especially for children raised in families with drug and biobehavioral disorders histories (Dawes *et al.*, 1997; Aytaclar *et al.*, 1999).

Vulnerability to Addiction

Drug abuse is a far more complex phenomenon than previously thought, and it is now recognized that drug abusers represent a highly heterogeneous group, and the patterns leading to dependence are diverse. Individual differences in temperament, social development, comorbidity, protective factors, and genetics are areas of intense research, and a detailed discussion of these contributions to addiction are beyond the scope of this book. However, each of these factors presumably interacts with the neurobiological processes discussed in this book. A reasonable assertion is that the initiation of drug abuse is more associated with social and environmental factors, whereas the movement to abuse and addiction are more associated with neurobiological factors (Glantz and Pickens, 1992).

Temperament and personality traits and some temperament clusters have been identified as factors of vulnerability to drug abuse (Glantz *et al.*, 1999) and include disinhibition (behavioral activation) (Windle and Windle, 1993), negative affect (Tarter *et al.*, 1995), novelty- and sensation-seeking (Wills *et al.*, 1994), and 'difficult temperament' (conduct disorder) (Glantz *et al.*, 1999).

From the perspective of comorbid psychiatric disorders, some of the strongest associations are found with mood disorders, anxiety disorders, antisocial personality disorders, and conduct disorders (Glantz and Hartel, 1999). Data from the International Consortium in Psychiatric Epidemiology (representing six different sites in the United States, Germany, Mexico, The Netherlands, Ontario, and Canada) and the National Comorbidity Study (United States; approximately 30 000 subjects) have revealed that approximately 35 per cent of the sample with drug dependence met lifetime criteria for a mood disorder. About 45 per cent met criteria for an anxiety disorder, and 50 per cent met criteria for either conduct or antisocial personality disorder (Merikangas *et al.*, 1998). More recent data on 12-month prevalence of comorbidity from the National Institute on Alcohol Abuse and Alcoholism's National Epidemiologic Survey on Alcohol and Related Conditions represents over 43 000 respondents and shows similar results (21–29 per cent for comorbidity of mood disorders; 22–25 per cent comorbidity for anxiety disorders; 32–70 per cent comorbidity for personality disorders) (Grant *et al.*, 2004a,b,c) (**Table 1.4**). The association of Attention Deficit Hyperactivity Disorder (ADHD) with drug abuse can be explained largely by the higher comorbidity with conduct disorder in these children (Biederman *et al.*, 1997). Independent of this association, there is little firm data to support a risk due to treatment of ADHD with stimulants (Biederman *et al.*, 1999), and no preference for stimulants over other drugs has been noted (Biederman *et al.*, 1997).

Developmental factors are important components of vulnerability, with strong evidence developing that adolescent exposure to alcohol, tobacco, or drugs of abuse leads to significant vulnerability for alcohol

TABLE 1.4 12-Month Prevalence of Comorbid Disorders Among Respondents with Nicotine Dependence, Alcohol Dependence, or Any Substance Use Disorder

	Mood	Anxiety	Personality
Alcohol	27.6%	23.5%	39.5%
Nicotine	21.1%	22.0%	31.7%
Substance Dependence (including alcohol but not nicotine)	29.2%	24.5%	69.5%

[Data from Grant *et al.*, 2004a,b,c.]