

# Neurocircuitry of Addiction

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Drug addiction is a chronically relapsing disorder that has been 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 (eg, dysphoria, anxiety, irritability) reflecting a motivational withdrawal syndrome when access to the drug is prevented. Drug addiction has been conceptualized as a disorder that involves elements of both impulsivity and compulsivity that yield a composite addiction cycle composed of three stages: 'binge/intoxication', 'withdrawal/negative affect', and 'preoccupation/anticipation' (craving). Animal and human imaging studies have revealed discrete circuits that mediate the three stages of the addiction cycle with key elements of the ventral tegmental area and ventral striatum as a focal point for the binge/intoxication stage, a key role for the extended amygdala in the withdrawal/negative affect stage, and a key role in the preoccupation/anticipation stage for a widely distributed network involving the orbitofrontal cortex–dorsal striatum, prefrontal cortex, basolateral amygdala, hippocampus, and insula involved in craving and the cingulate gyrus, dorsolateral prefrontal, and inferior frontal cortices in disrupted inhibitory control. The transition to addiction involves neuroplasticity in all of these structures that may begin with changes in the mesolimbic dopamine system and a cascade of neuroadaptations from the ventral striatum to dorsal striatum and orbitofrontal cortex and eventually dysregulation of the prefrontal cortex, cingulate gyrus, and extended amygdala. The delineation of the neurocircuitry of the evolving stages of the addiction syndrome forms a heuristic basis for the search for the molecular, genetic, and neuropharmacological neuroadaptations that are key to vulnerability for developing and maintaining addiction.

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## CONCEPTUAL FRAMEWORK

### Addiction Definitions: Drug Use, Abuse, and Dependence Addiction Cycle

Drug addiction is a chronically relapsing disorder that has been 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 (eg, dysphoria, anxiety, irritability) reflecting a motivational withdrawal syndrome when access to the drug is prevented (defined as Substance Dependence by the *Diagnostic and Statistical Manual of Mental Disorders* [DSM] of the American Psychiatric Association; Koob and Le Moal, 1997; Table 1). The occasional but limited use of an abusable drug is clinically distinct from escalated drug use, loss of control over limiting drug intake, and the emergence of chronic compulsive drug-seeking that characterizes addiction. The

critical nature of the distinction between drug use, abuse, and dependence has been illuminated by data showing that approximately 15.6% (29 million) of the US adult population will go on to engage in nonmedical or illicit drug use at some time in their lives, with approximately 2.9% (5.4 million) going on to substance dependence on illicit drugs (Grant and Dawson, 1998; Grant *et al.*, 2004). For alcohol, 51% (120 million) of people over the age of 12 were current users, and of these current users, 7.7% (18 million) met the criteria for Substance Abuse or Dependence on Alcohol. For nicotine, in 2007, approximately 28.6% (70.9 million) Americans aged 12 or older were current (past month) users of a tobacco product, and of these current users, 24.2% (60.1 million) were current cigarette smokers; 5.4% (13.3 million) smoked cigars; 3.2% (8.1 million) used smokeless tobacco; and 0.8% (2.0 million) smoked tobacco in pipes (Substance Abuse and Mental Health Services Administration, 2008).

Although 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 now is shifting to chronic administration and the acute and long-term neuroadaptive changes in the brain

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Table 1 Definitions

<i>Addiction</i>	Assumed to be identical to the syndrome of Substance Dependence (as currently defined by the <i>Diagnostic and Statistical Manual of Mental Disorders</i> ; American Psychiatric Association, 1994), and Substance Dependence on Alcohol is assumed to be identical to alcoholism. In this paper, we favor the term 'addiction' rather than dependence to avoid confusion with 'physical dependence,' which refers to the physical adaptations that result in largely somatic withdrawal symptoms when drugs such as alcohol, heroin, and benzodiazepines are abruptly discontinued. The adaptations associated with physical drug withdrawal are distinct from the motivational changes of acute withdrawal and protracted abstinence.
<i>Impulsivity</i>	Defined behaviorally as 'a predisposition toward rapid, unplanned reactions to internal and external stimuli without regard for the negative consequences of these reactions to themselves or others' (Moeller <i>et al</i> , 2001). Impulsivity is often measured in two domains: the choice of a smaller, immediate reward over a larger, delayed reward (Rachlin and Green, 1972) or the inability to inhibit behavior by changing the course of action or to stop a response once it is initiated (Logan <i>et al</i> , 1997). Impulsivity is a core deficit in substance abuse disorders (Allen <i>et al</i> , 1998).
<i>Compulsivity</i>	Defined as elements of behavior that result in perseveration in responding in the face of adverse consequences, perseveration in responding in the face of incorrect responses in choice situations, or persistent reinitiation of habitual acts (Everitt and Robbins, 2005). The elements of compulsivity are represented in many of the symptoms outlined in the DSM-IV: continued substance use despite knowledge of having had a persistent or recurrent physical or psychological problem and a great deal of time spent in activities necessary to obtain the substance (American Psychiatric Association, 2000).
<i>Positive reinforcement</i>	Defined as the process by which presentation of a stimulus, usually pleasant (eg, the drug itself), increases the probability of a response.
<i>Negative reinforcement</i>	Defined as the process by which removal of an aversive stimulus (eg, negative emotional state of drug withdrawal) increases the probability of a response (eg, dependence-induced drug intake).
<i>Automaticity</i>	Defined as behaviors that occur without conscious awareness of intentionality.
<i>Motivation</i>	Defined as a 'tendency of the whole animal to produce organized activity' (Hebb, 1972).
<i>Intracranial self-administration</i>	A procedure whereby drugs injected directly into the brain in minute amounts serve as positive reinforcers.
<i>place conditioning</i>	A procedure whereby drugs directed into the brain are paired with a specific environment and vehicle with another environment. Subsequently, the animal is tested for its preference for the paired environment or the nonpreferred environment.
<i>Second-order schedule of reinforcement</i>	A procedure in which an animal is trained to work for a drug under conditions of two components. In the first component, a previously neutral stimulus such as a light or tone is delivered under certain requirements (eg, each stimulus is delivered after 10 lever presses). In the second component, the drug is delivered after the last 10th response after 15 min has elapsed (Arroyo <i>et al</i> , 1998).

that result in relapse. The purpose of current neurobiological drug abuse research is to understand the genetic/epigenetic, 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 and to chronic relapse even after protracted abstinence which is a hallmark of addiction.

A psychiatric-motivational framework that provides sources of both positive and negative reinforcement for drug-taking is the conceptualization that drug addiction has aspects of both impulse control disorders and compulsive disorders (Table 1). Impulse control disorders are characterized by an increasing sense of tension or arousal before committing an impulsive act and pleasure, gratification, or relief at the time of committing the act. Impulse control disorders are largely associated with positive reinforcement mechanisms (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. Compulsive disorders are largely associated with negative reinforcement mechanisms and automaticity.

Collapsing the cycles of impulsivity and compulsivity yields a composite addiction cycle composed of three stages—binge/intoxication, withdrawal/negative affect, preoccupation/anticipation—in which impulsivity often

dominates at the early stages and impulsivity combined with compulsivity dominates at the later stages. As an individual moves from impulsivity to compulsivity, a shift occurs from positive reinforcement driving the motivated behavior to negative reinforcement and automaticity driving the motivated behavior (Koob, 2004; Table 1). These three stages are conceptualized as interacting with each other, becoming more intense, and ultimately leading to the pathological state known as addiction (Koob and Le Moal, 1997; Table 2). The transition from occasional drug use to addiction involves neuroplasticity in all of these elements and may begin with initial drug use in vulnerable individuals or individuals at particularly vulnerable developmental periods (eg, adolescence; Koob *et al*, 2008b). The present review focuses on the brain neurocircuitry that is engaged at each stage of the addiction cycle, how it changes with increasing engagement with drugs of abuse, and how it interacts to produce the pathological state known as addiction.

### Sources of Reinforcement: Motivation, Opponent Process, Incentive Salience

Changes in the motivation for drugs and natural rewards are a key component of addiction (Table 1). Early work by Wikler (1952) stressed the function of changes in drive states associated with dependence (herein referred to as

**Table 2** Animal Laboratory Models of The Different Stages of The Addiction Cycle

Stage of addiction cycle	Animal models	Reference
<i>Binge/Intoxication</i>	Drug/alcohol self-administration	Collins <i>et al</i> , 1984
	Conditioned place preference	Sanchis-Segura and Spanagel, 2006
	Brain stimulation reward thresholds	Kornetsky and Bain, 1990
<i>Withdrawal/Negative affect</i>	Anxiety-like responses	Samyai <i>et al</i> , 1995; Schulteis <i>et al</i> , 1998; Baldwin <i>et al</i> , 1991
<i>Preoccupation/Anticipation</i>	Conditioned place aversion	Tzschentke, 1998
	Elevated reward thresholds	Markou <i>et al</i> , 1998
	Increased motivation for self-administration in dependent animals	Ahmed and Koob, 1998; Ahmed <i>et al</i> , 2000; Roberts <i>et al</i> , 2000; Kitamura <i>et al</i> , 2006; O'Dell and Koob, 2007; Tomatzky and Miczek, 2000; Ahmed and Koob, 1998; Deroche-Gamonet <i>et al</i> , 2004; Vanderschuren and Everitt, 2004
	Drug-induced reinstatement	Sanchis-Segura and Spanagel, 2006
<i>Anticipation</i>	Cue-induced reinstatement	Sanchis-Segura and Spanagel, 2006
	Stress-induced reinstatement	Sanchis-Segura and Spanagel, 2006

Taken with permission from Koob *et al* (2009).

addiction. Subjects described withdrawal changes as a 'hunger' or primary need and the effects of morphine on such a state as 'satiation' or gratification of the primary need (Wikler, 1952). Although Wikler argued that positive reinforcement was retained even in heavily dependent subjects (eg, thrill of the intravenous opioid injection), addiction produced a new source of gratification, that of negative reinforcement (Table 1).

The concept of motivation was linked inextricably with hedonic, affective, or emotional states in the transition to addiction by Solomon's opponent process theory of motivation. Solomon and Corbit (1974) postulated that hedonic, affective, or emotional states, once initiated, are automatically modulated by the central nervous system with mechanisms that reduce the intensity of hedonic feelings. Positive hedonic responses in drug use occur shortly after presentation of a stimulus, correlate closely with the intensity, quality, and duration of the reinforcer, and show tolerance and affective or hedonic withdrawal (abstinence). In contrast, negative hedonic responses follow the positive hedonic responses, are sluggish in onset, slow to build up to an asymptote, slow to decay, and get larger with repeated exposure. The role of opponent processes begins early in drug-taking, reflects changes in the brain reward and stress systems, and later forms one of the major motivations for compulsivity in drug-taking in the form of a motivational withdrawal syndrome.

In this formulation, manifestation of a withdrawal syndrome after removal of chronic drug administration, either acute or protracted, is defined in terms of motivational aspects of dependence such as the emergence of a negative emotional state (eg, dysphoria, anxiety, irritability) when access to the drug is prevented (Koob and Le Moal, 2001), rather than on the physical signs of dependence, which tend to be of short duration. Indeed, some have

argued that the development of such a negative affective state can define dependence relative to addiction (Russell, 1976; Baker *et al*, 1987) and that such a negative affective state contributes to compulsivity through negative reinforcement mechanisms (Koob and Le Moal, 2005).

Another conceptualization of the motivational changes associated with addiction is derived from early work on conditioned reinforcement, incentive motivation, behavioral sensitization, and maladaptive stimulus-response learning, all of which are subsumed under the motivational conceptualization of incentive salience. Drugs are hypothesized to usurp systems in the brain that are put in place to direct animals to stimuli with salience for preservation of the species. The incentive salience hypothesis has significant heuristic value as a common element of drug addiction because it narrows the focus to drug-seeking at the expense of natural rewards. The clinical observation that individuals with substance use disorders have an unusual focus on drug-seeking to the exclusion of natural rewards fits the incentive salience view.

The increase in incentive salience produced by psychostimulant drugs has early roots in the facilitation of conditioned reinforcement and drug-seeking (Robbins, 1976; Hill, 1970). Here, drug-seeking is controlled by a succession of drug-associated discriminative stimuli that can also function as conditioned reinforcers when presented as a consequence of instrumental responses (Everitt *et al*, 2008). Many have argued that by means of associative learning, the enhanced incentive salience state becomes oriented specifically toward drug-related stimuli, leading to escalating compulsion for seeking and taking drugs (Hyman *et al*, 2006; Kalivas and Volkow, 2005). The underlying activation of neural structures involved in maintaining the incentive salience state persists, making addicts vulnerable to long-term relapse.

Another view of incentive salience involved behavioral sensitization, usually measured as increased locomotor responses to repeated administration of a drug. The behavioral sensitization paradigm has provided a major impetus to exploring not only the neurocircuitry of addiction but also a model of the neuroplasticity that may occur during the transition from drug use to addiction. Here, a shift in an incentive salience state, described as 'wanting' linked to compulsive use, as opposed to 'liking' linked to hedonic responses, was hypothesized to be progressively increased by repeated exposure to drugs of abuse (Robinson and Berridge, 1993).

### Transition to Addiction: Patterns of Drug-Taking, Animal Models

Different drugs produce different patterns of neuroadaptations with chronic drug exposures. For example, opioid-addicted subjects meet most of the DSM criteria for addiction, including dramatic tolerance and withdrawal (classic symptoms associated with physical dependence) and most of the symptoms associated with motivational withdrawal. A pattern of intravenous or smoked drug-taking evolves, including intoxication, tolerance, escalation in intake, and profound dysphoria, physical discomfort, and somatic withdrawal signs during abstinence. Intense preoccupation with obtaining opioids (craving) develops that often precedes the somatic signs of withdrawal and is linked not only to stimuli associated with obtaining the drug but also to stimuli associated with withdrawal and the aversive motivational state. A pattern develops in which the drug must be obtained to avoid the severe dysphoria and discomfort of abstinence. Other drugs of abuse follow a similar pattern but may involve more the binge/intoxication stage (psychostimulants) or less binge/intoxication and more withdrawal/negative affect and preoccupation/anticipation stages (nicotine and cannabinoids).

Much of the recent progress in understanding the neurobiology of addiction has derived from the study of animal models of addiction to specific drugs such as stimulants, opioids, alcohol, nicotine, and  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC). Although no animal model of addiction fully emulates the human condition, animal models do permit investigation of specific elements of the process of drug addiction. Such elements can be defined by models of different stages of the addiction cycle (see above; Table 2).

A progressive increase in the frequency and intensity of drug use is one of the major behavioral phenomena characterizing the development of addiction and has face validity with the DSM criteria: 'The substance is often taken in larger amounts and over a longer period than was intended' (American Psychiatric Association, 1994). Two animal models, one involving experimenter-administered drug, and the other involving self-administered drug, have been used to explore the effects of repeated drug administration on neuroplasticity in the neurocircuits identified

above. Behavioral sensitization typically involved repeated administration by the experimenter of a drug, usually a psychostimulant, in a specific environmental context and the dependent measure was usually locomotor activity. Here, animals that received drug showed a much more dramatic increase in locomotor activity to a challenge dose of drug (sensitization) than controls that had received only repeated measures of vehicle injections.

A framework, perhaps with more face validity with which to model the transition from drug use to drug addiction, can be found in animal models of prolonged access to self-administration of drugs. Here, using intravenous drug self-administration, extended access to drugs is associated with an escalation in intake over days (Koob, 2009a). Such increased self-administration also has been observed with alcohol in which rats drink excessively during acute and protracted withdrawal from dependence induction using either chronic liquid diet or chronic vapor exposure (Gilpin and Koob, 2008). Animals made dependent on alcohol reliably obtain blood alcohol levels in the 100–150 mg% range, which are equivalent to the levels abused by moderate to heavy alcohol abusers. Changes in the reinforcing and incentive effects of the drug have been observed following extended access and induction of dependence and include increased progressive-ratio responding (Koob, 2009a), increased drug-induced reinstatement after extinction, decreased latency to goal time in a runway model for drug reward (Deroche-Gamonet *et al*, 2004), and increased resistance to punishment in which the animal will sustain higher aversive punishment to obtain drug (Vanderschuren and Everitt, 2004). Whether the enhanced drug-taking with extended access reflects a sensitization of reward (or of incentive motivation) or a reward-deficit state, or both, remains under discussion (Vezina, 2004).

## NEUROCIRCUITRY OF ADDICTION: NEUROPSYCHOPHARMACOLOGICAL EVIDENCE FROM ANIMAL STUDIES

### Binge/Intoxication Stage

Our understanding of the neurobiological substrates for the reinforcing effects of drugs of abuse can be traced to early work on the identification of a reward system in the brain with the discovery of electrical brain stimulation reward or intracranial self-stimulation by Olds and Milner (1954). Brain stimulation reward involves widespread neurocircuitry in the brain, but the most sensitive sites defined by the lowest thresholds involve the trajectory of the medial forebrain bundle that connects the ventral tegmental area (VTA) to the basal forebrain (Olds and Milner, 1954). All drugs of abuse, when administered acutely, decrease brain stimulation reward thresholds (ie, increased reward; Kornetsky and Esposito, 1979) and when administered chronically increase reward thresholds during withdrawal (ie, decreased reward; see below). Although much emphasis



was focused initially on the role of the ascending monoamine systems in the medial forebrain bundle in reward, first norepinephrine (Stein, 1962) and then dopamine (Crow, 1973; Wise, 1978), other nondopaminergic systems in the medial forebrain bundle clearly have a key role in mediating brain stimulation reward (Hernandez *et al*, 2006). Indeed, much work suggests that activation of the midbrain dopamine system has multiple roles to give incentive salience to stimuli in the environment (Robinson and Berridge, 1993) to promote performance of goal-directed behavior (Salamone *et al*, 2007) or activation in general (Le Moal and Simon, 1991). More recently, the hypothesis has been raised that the time course of dopamine signaling is a key factor, with the fastest time course predominantly having a preferential role in reward and valuation of predicted outcomes of behavior and steady activation of dopamine release having a preferential role in providing an enabling effect on specific behavior-related systems (Schultz, 2007). Work in the domain of the acute reinforcing effects of drugs of abuse supports this hypothesis in which the mesolimbic dopamine system is critical for the acute rewarding effects of psychostimulant drugs but has a more enabling function for all drugs of abuse.

The acute rewarding properties of psychostimulant drugs have long been known to depend on activation of the mesolimbic dopamine system, but activation of this system is not necessarily critical for the acute reinforcing effects of other drugs of abuse (Koob, 1992; Nestler, 2005; Hnasko *et al*, 2005). Neurotoxin-selective lesions of the mesocorticolimbic dopamine system block the reinforcing effects of cocaine and D-amphetamine (McGregor and Roberts, 1993). In contrast, neurochemically specific lesions of dopamine in the nucleus accumbens with 6-hydroxydopamine failed to block heroin or ethanol self-administration, supporting this hypothesis (Koob and Le Moal, 2006).

Using the technique of intracranial self-administration (Table 1) and intracranial place conditioning (Table 1), opioids and alcohol have been shown to be directly self-administered into the VTA. Opioids also produce conditioned place preference when injected into the VTA. Opioids, phencyclidine, and psychostimulants are directly self-administered into the nucleus accumbens, and psychostimulants produce a conditioned place preference when injected into the nucleus accumbens. Cocaine and phencyclidine are directly self-administered into the frontal cortex (McBride *et al*, 1999). The mesolimbic dopamine system is activated by acute administration of opioids, ethanol, nicotine, and  $\Delta^9$ -THC (Di Chiara and Imperato, 1988).

Intravenous nicotine self-administration is blocked by neurotoxin-specific lesions of the mesocorticolimbic dopamine system, and the neuropharmacological action has been hypothesized to be through nicotinic receptor activation of release of dopamine primarily in the VTA and also presynaptically in the nucleus accumbens (Watkins *et al*, 2000). However, nicotine reward measured by conditioned place preference appears to be independent of the mesocorticolimbic dopamine system (Laviolette *et al*,

2002). Other substrates implicated in nicotine reward include cholinergic inputs to the pedunclopontine nucleus (Yeomans and Baptista, 1997). In the VTA, activation of the  $\beta 2$  subunit of nicotinic receptors appears to be critical for nicotine activation of dopamine neurons (Mameli-Engvall *et al*, 2006). Neuropharmacological studies on cannabinoids have implicated both cannabinoid and opioid mechanisms. Opioid and cannabinoid CB<sub>1</sub> antagonists block intravenous self-administration of  $\Delta^9$ -THC in squirrel monkeys (Justina *et al*, 2003). Similar to other drugs of abuse,  $\Delta^9$ -THC administration activates dopamine release in the nucleus accumbens shell (Tanda *et al*, 1997).

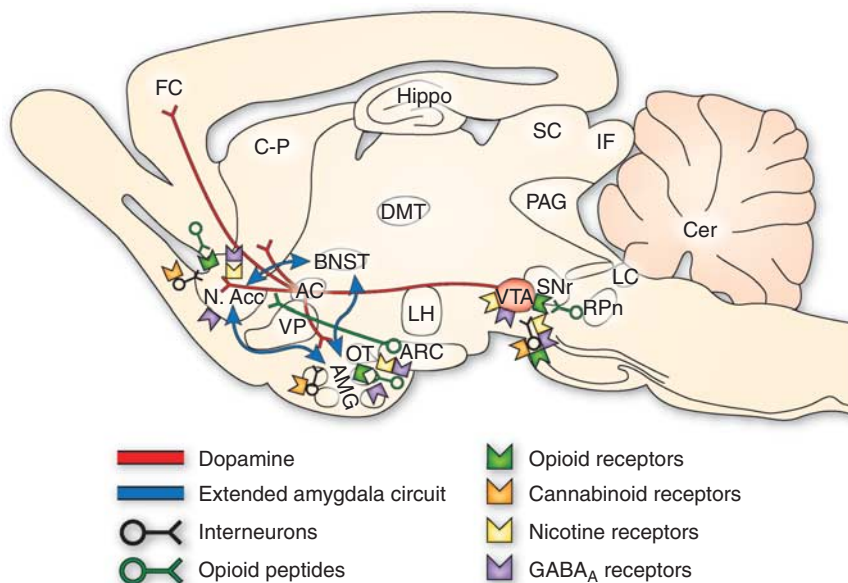
Thus, all drugs of abuse activate the mesolimbic dopamine system, but much evidence suggests that dopamine-independent reinforcement occurs at the level of the nucleus accumbens, suggesting multiple inputs to the activation of critical reinforcement circuitry in these brain regions (Koob, 1992; Nestler, 2005).

The central nucleus of the amygdala (CeA) also has a key function in the acute reinforcing actions of drugs of abuse. Microinjections of dopamine D<sub>1</sub> receptor antagonists into the CeA block cocaine self-administration (Caine *et al*, 1995; McGregor and Roberts, 1993). The most sensitive site for  $\gamma$ -aminobutyric acid (GABA) and opioid antagonism of oral alcohol self-administration in nondependent rats was the CeA (Hyytia and Koob, 1995; Heyser *et al*, 1999). Lesions of the CeA block oral self-administration of alcohol (Moller *et al*, 1997). Serotonin-3 antagonists injected into the CeA block oral ethanol self-administration in nondependent rats, an effect hypothesized to possibly involve the ability of serotonin-3 receptor antagonists to block drug-induced dopamine release (Dyr and Kostowski, 1995).

A major output from the nucleus accumbens is to the ventral pallidum/substantia innominata. Consistent with the nucleus accumbens as a key substrate for drug reward, lesions of the ventral pallidum are particularly effective in blocking the motivation to work for intravenous cocaine and intravenous heroin (Hubner and Koob, 1990; Robledo and Koob, 1993). In addition, blockade of dopamine and GABA<sub>A</sub> receptors in the ventral pallidum blocks the reinforcing effects of alcohol (Melendez *et al*, 2004; June *et al*, 2003). Thus, elements of the ventral pallidum may not only be critical for further processing of the drug reward signal but may also be directly modulated by drugs of abuse.

The dorsal striatum does not appear to have a major role in the acute reinforcing effects of drugs of abuse but appears to be recruited during the development of compulsive drug-seeking (Everitt *et al*, 2008). 6-Hydroxydopamine lesions of the dorsal striatum do not block cocaine-induced locomotor activity or cocaine self-administration (Roberts, 1992) but do block amphetamine-induced stereotyped behavior (Kelly and Iversen, 1976; Creese and Iversen, 1974). Using a second-order schedule (Table 1), lesions of the nucleus accumbens and basolateral amygdala blocked the acquisition of cocaine-seeking (Whitelaw *et al*, 1996). Similarly, when the nucleus accumbens core was selectively lesioned on one side of the brain and combined with

## Neurochemical neurocircuits in drug reward



**Figure 1.** Sagittal section through a representative rodent brain illustrating the pathways and receptor systems implicated in the acute reinforcing actions of drugs of abuse. Cocaine and amphetamines activate the release of dopamine in the nucleus accumbens and amygdala through direct actions on dopamine terminals. Opioids activate opioid receptors in the VTA, nucleus accumbens, and amygdala through direct or indirect actions via interneurons. Opioids facilitate the release of dopamine in the nucleus accumbens by an action either in the VTA or the nucleus accumbens, but also are hypothesized to activate elements independent of the dopamine system. Alcohol activates  $\gamma$ -aminobutyric acid-A ( $GABA_A$ ) receptors or  $GABA$  release in the VTA, nucleus accumbens, and amygdala by either direct actions at the  $GABA_A$  receptor or through indirect release of  $GABA$ . Alcohol is hypothesized to facilitate the release of opioid peptides in the VTA, nucleus accumbens, and central nucleus of the amygdala. Alcohol facilitates the release of dopamine in the nucleus accumbens through an action either in the VTA or the nucleus accumbens. Nicotine activates nicotinic acetylcholine receptors in the VTA, nucleus accumbens, and amygdala, either directly or indirectly, through actions on interneurons. Cannabinoids activate cannabinoid  $CB_1$  receptors in the VTA, nucleus accumbens, and amygdala. Cannabinoids facilitate the release of dopamine in the nucleus accumbens through an unknown mechanism either in the VTA or the nucleus accumbens. The blue arrows represent the interactions within the extended amygdala system hypothesized to have a key function in drug reinforcement. The medial forebrain bundle represents ascending and descending projections between the ventral forebrain (nucleus accumbens, olfactory tubercle, septal area) and the ventral midbrain (VTA) (not shown in figure for clarity). AC, anterior commissure; AMG, amygdala; ARC, arcuate nucleus; BNST, bed nucleus of the stria terminalis; Cer, cerebellum; C-P, caudate-putamen; DMT, dorsomedial thalamus; FC, frontal cortex; Hippo, hippocampus; IF, inferior colliculus; LC, locus coeruleus; LH, lateral hypothalamus; N. Acc., nucleus accumbens; OT, olfactory tract; PAG, periaqueductal gray; RPh, reticular pontine nucleus; SC, superior colliculus; SNr, substantia nigra pars reticulata; VP, ventral pallidum; VTA, ventral tegmental area (taken with permission from Koob, 2005).

dopamine receptor blockade in the contralateral dorsal striatum, no effect was observed in animals immediately after acquisition, but greatly decreased cocaine-seeking was observed in rats with stable responding on a second-order schedule (Belin and Everitt, 2008). These results suggest that the dorsal striatum may have a minor role in the acute reinforcing effects of psychostimulant drugs but a key role in the transition to compulsive use (Everitt *et al*, 2008).

Data with knockout mice also provide key insights into the role of dopamine in the rewarding effects of drugs of abuse. Genetically altered mice homozygous with a lack of the dopamine  $D_1$  receptor do not self-administer cocaine (Caine *et al*, 2007). Although the initial report that dopamine transporter (DAT) knockout mice continued to self-administer cocaine (Rocha *et al*, 1998) questioned the function of the DAT in cocaine's reinforcing effects, a recent study showed that transgenic animals that expressed DAT that did not bind cocaine but that was functional as a dopamine reuptake carrier did not show cocaine reward measured by conditioned place preference (Chen *et al*,

2006a). These results support the hypothesis of a crucial role of the DAT in cocaine's reinforcing effects.

On the basis of this synthesis, an early neurobiological circuit for drug reward was proposed (Koob, 1992) that has been elaborated and expanded (Koob and Nestler, 1997; Figure 1). The starting point for the reward circuit was the medial forebrain bundle, composed of myelinated fibers connecting bidirectionally the olfactory tubercle and nucleus accumbens with the hypothalamus and VTA (Nauta and Haymaker, 1969) and including the ascending monoamine pathways such as the mesocorticolimbic dopamine system.

The initial action of drug reward was hypothesized to depend on dopamine release in the nucleus accumbens for cocaine, amphetamine, and nicotine; opioid peptide receptor activation in the VTA (dopamine activation) and nucleus accumbens (independent of dopamine activation) for opiates; and  $GABA_A$  systems in the nucleus accumbens and amygdala for alcohol. The nucleus accumbens is situated strategically to receive important limbic information

from the amygdala, frontal cortex, and hippocampus that could be converted to motivational action through its connections with the extrapyramidal motor system. Thus, an early critical role for the nucleus accumbens was established for the acute reinforcing effects of drugs, with a supporting role for the CeA and ventral pallidum (Figures 1 and 2a).

### Withdrawal/Negative Affect Stage

The neuroanatomical entity termed the extended amygdala (Heimer and Alheid, 1991) may represent a common anatomical substrate integrating brain arousal-stress systems with hedonic processing systems to produce the negative emotional states that promote negative reinforcement mechanisms associated with the development of addiction. The extended amygdala is composed of the CeA, bed nucleus of the stria terminalis (BNST), and a transition zone in the medial (shell) subregion of the nucleus accumbens (Figure 2b). Each of these regions has cytoarchitectural and circuitry similarities (Heimer and Alheid, 1991). The extended amygdala receives numerous afferents from limbic structures such as the basolateral amygdala and hippocampus and sends efferents to the medial part of the ventral pallidum and a large projection to the lateral hypothalamus, thus further defining the specific brain areas that interface classical limbic (emotional) structures with the output of extrapyramidal motor system (Alheid *et al*, 1995). The extended amygdala has long been hypothesized to have a key role not only in fear conditioning (Le Doux, 2000) but also in the emotional component of pain processing (Neugebauer *et al*, 2004).

Within-system neuroadaptations to chronic drug exposure include decreases in function of the neurotransmitter systems in the neurocircuits implicated in the acute reinforcing effects of drug of abuse. One prominent hypothesis is that dopamine systems are compromised in crucial phases of the addiction cycle, such as withdrawal, and lead to decreased motivation for nondrug-related stimuli and increased sensitivity to the abused drug (Melis *et al*, 2005; see brain imaging studies below). Psychostimulant withdrawal in humans is associated with fatigue, decreased mood and psychomotor retardation, and in animals is associated with decreased motivation to work for natural rewards (Barr and Phillips, 1999) and decreased locomotor activity (Pulvirenti and Koob, 1993), behavioral effects that may involve decreased dopaminergic function. Animals during amphetamine withdrawal show decreased responding on a progressive-ratio schedule for a sweet solution, and this decreased responding was reversed by the dopamine partial agonist terguride (Orsini *et al*, 2001), suggesting that low dopamine tone contributes to the motivational deficits associated with psychostimulant withdrawal. Decreases in activity of the mesolimbic dopamine system and decreases in serotonergic neurotransmission in the nucleus accumbens occur during acute drug withdrawal

from all major drugs of abuse in animal studies (Rossetti *et al*, 1992; Weiss *et al*, 1992, 1996).

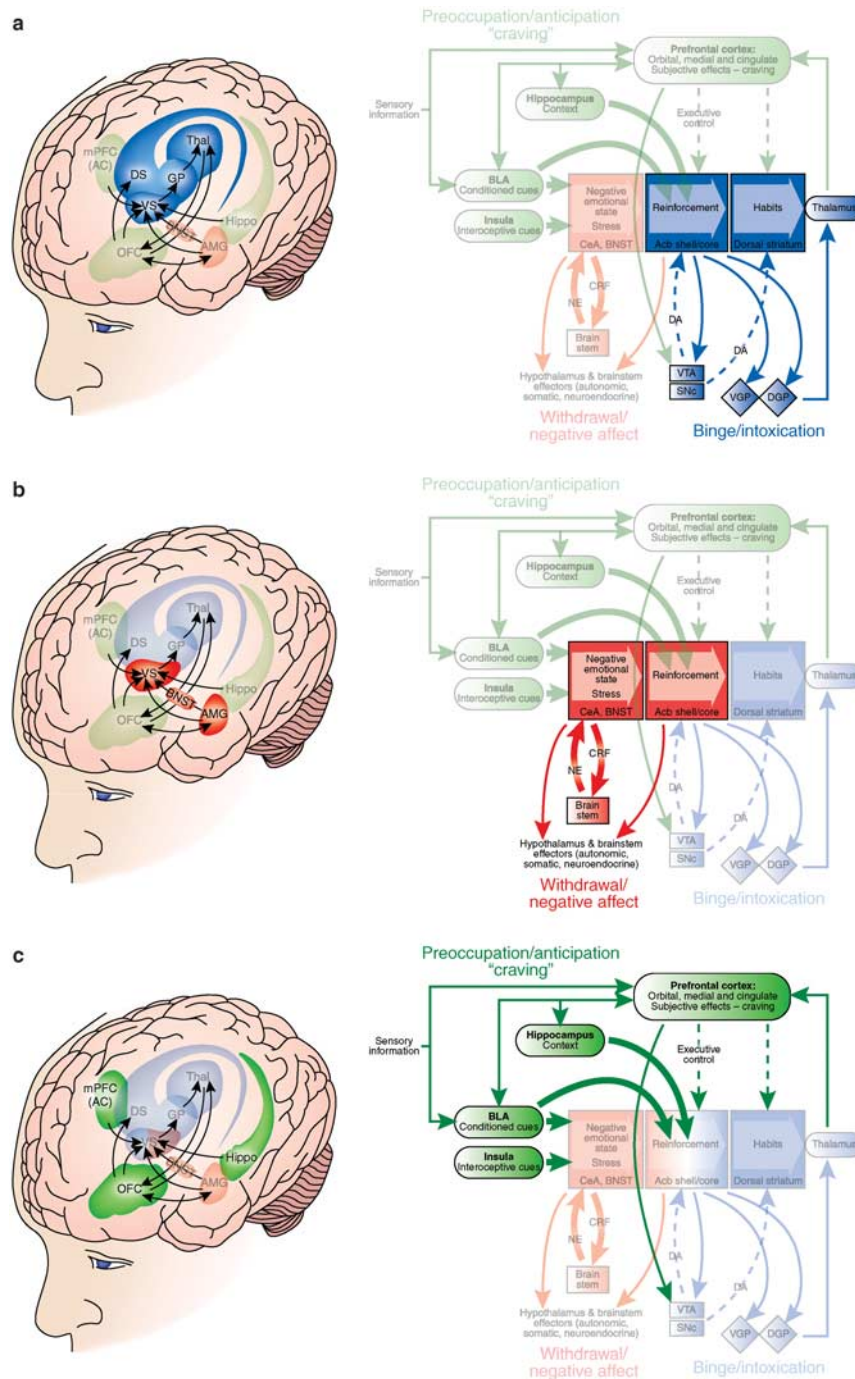
A second component of the withdrawal/negative affect stage is a between-system neuroadaptation in which different neurochemical systems involved in stress modulation also may be engaged within the neurocircuitry of the brain stress and aversive systems in an attempt to overcome the chronic presence of the perturbing drug to restore normal function despite the presence of drug. Both the hypothalamic-pituitary-adrenal axis and the brain stress/aversive system mediated by corticotropin-releasing factor (CRF) are activated during withdrawal from chronic administration of all major drugs with abuse potential, with a common response of elevated adrenocorticotropic hormone, corticosterone, and amygdala CRF during acute withdrawal (Koob, 2008; Koob and Kreek, 2007). Acute withdrawal from all drugs of abuse also produces an aversive or anxiety-like state in which CRF and other stress-related systems (including noradrenergic pathways) have key roles.

The aversive stimulus effects of drug withdrawal can be measured using place aversion (Hand *et al*, 1988), and the opioid partial agonist buprenorphine dose dependently decreased the place aversion produced by precipitated opioid withdrawal. Systemic administration of a CRF<sub>1</sub> receptor antagonist and direct intracerebral administration of a peptide CRF<sub>1</sub>/CRF<sub>2</sub> antagonist also decreased opioid withdrawal-induced place aversions (Stinus *et al*, 2005; Heinrichs *et al*, 1995). Functional noradrenergic antagonists administered directly into the BNST blocked opioid withdrawal-induced place aversion, implicating the importance of noradrenergic stimulation in the stress responses that follow acute drug withdrawal (Delfs *et al*, 2000). Indeed, classical medications used to treat physical withdrawal in heroin abusers and alcoholics include  $\alpha$ -adrenergic drugs (eg, clonidine) that inhibit noradrenergic release and decrease some symptoms of alcohol and heroin withdrawal.

Another candidate for the aversive effects of drug withdrawal is dynorphin. Much evidence shows that dynorphin is increased in the nucleus accumbens in response to dopaminergic activation and, in turn, that overactivity of the dynorphin systems can decrease dopaminergic function.  $\kappa$ -Opioid agonists are aversive, and cocaine, opioid, and ethanol withdrawal is associated with increased dynorphin in the nucleus accumbens and/or amygdala (Koob, 2008). An exception is salvidorin A, which is a  $\kappa$ -agonist abused by humans, but this may reflect its hallucinogenic effects rather than any pleasurable properties (Gonzalez *et al*, 2006).

Another common between-system response to acute withdrawal and protracted abstinence from all major drugs of abuse is the manifestation of anxiety-like responses. For example, withdrawal from repeated administration of cocaine produces an anxiogenic-like response in the elevated plus maze and defensive burying test, both of which are reversed by CRF antagonists. Similarly, ethanol withdrawal produces anxiety-like behavior that is reversed





**Figure 2.** Neural circuitry associated with the three stages of the addiction cycle. (a) Binge/intoxication stage. Reinforcing effects of drugs may engage reward neurotransmitters and associative mechanisms in the nucleus accumbens shell and core and then engage stimulus–response habits that depend on the dorsal striatum. Two major neurotransmitters mediating the rewarding effects of drugs of abuse are dopamine and opioid peptides. (b) Withdrawal/negative affect stage. The negative emotional state of withdrawal may engage the activation of the extended amygdala. The extended amygdala is composed of several basal forebrain structures, including the bed nucleus of the stria terminalis, central nucleus of the amygdala, and possibly a transition zone in the medial portion (or shell) of the nucleus accumbens. Major neurotransmitters in the extended amygdala hypothesized to have a function in negative reinforcement are corticotropin-releasing factor, norepinephrine, and dynorphin. Major projections of the extended amygdala are to the hypothalamus and brainstem. (c) Preoccupation/anticipation (craving) stage. This stage involves the processing of conditioned reinforcement in the BLA and the processing of contextual information by the hippocampus. Executive control depends on the prefrontal cortex and includes representation of contingencies, representation of outcomes, and their value and subjective states (ie, craving and, presumably, feelings) associated with drugs. The subjective effects termed drug craving in humans involve activation in functional imaging studies of the orbital and anterior cingulate cortices and temporal lobe, including the amygdala. A major neurotransmitter involved in the craving stage is glutamate localized in pathways from frontal regions and the BLA that project to the ventral striatum. Green/blue arrows, glutamatergic projections; orange arrows, dopaminergic projections; pink arrows, GABAergic projections; Acb, nucleus accumbens; BLA, basolateral amygdala; VTA, ventral tegmental area; SNc, substantia nigra pars compacta; VGP, ventral globus pallidus; DGP, dorsal globus pallidus; BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; NE, norepinephrine; CRF, corticotropin-releasing factor; PIT, Pavlovian instrumental transfer (modified with permission from Koob *et al*, 2008a).



by intracerebroventricular administration of CRF<sub>1</sub>/CRF<sub>2</sub> peptidergic antagonists, systemic administration of a small molecule CRF<sub>1</sub> antagonist, and microinjection of a peptidergic CRF<sub>1</sub>/CRF<sub>2</sub> antagonist into the amygdala (Funk *et al*, 2006; Koob, 2008). CRF antagonists injected intracerebroventricularly or systemically also block the potentiated anxiety-like responses to stressors observed during protracted abstinence from chronic ethanol, and the effects of CRF antagonists have been localized to the CeA (Koob, 2008). Precipitated withdrawal from nicotine produces anxiety-like responses that are also reversed by CRF antagonists (Tucci *et al*, 2003; George *et al*, 2007).

Thus, acute withdrawal is associated with within-system changes reflected in a decrease in dopaminergic activity in the mesolimbic dopamine system and with between-system recruitment of neurotransmitter systems that convey stress and anxiety-like effects such as CRF and dynorphin. Other neurotransmitter systems known to be involved in emotional dysregulation of the motivational effects of drug withdrawal include norepinephrine, substance P, vasopressin, neuropeptide Y (NPY), endocannabinoids, and nociceptin (Koob, 2008).

### Preoccupation/Anticipation (Craving) Stage

The preoccupation/anticipation or craving stage of the addiction cycle has long been hypothesized to be a key element of relapse in humans and defines addiction as a chronic relapsing disorder. Although often linked to the construct of craving, craving *per se* has been difficult to measure clinically (Tiffany *et al*, 2000) and often does not correlate well with relapse. Nevertheless, the stage of the addiction cycle in which the individual reinstates drug-seeking behavior after abstinence remains a challenging focus for neurobiological mechanisms and medications development for treatment. Animal models of craving can be divided into two domains: drug-seeking induced by drug or stimuli paired with drug-taking, and drug-seeking induced by an acute stressor or a residual negative emotional state, often a state of stress, termed protracted abstinence (see Transition to addiction: patterns of drug-taking, animal models section).

Much evidence from animal studies suggests that drug-induced reinstatement is localized to the medial prefrontal cortex/nucleus accumbens/ventral pallidum circuit mediated by the neurotransmitter glutamate (McFarland and Kalivas, 2001). In contrast, cue-induced reinstatement appears to involve the basolateral amygdala as a critical substrate with a possible feed-forward mechanism through the prefrontal cortex system involved in drug-induced reinstatement (Everitt and Wolf, 2002; Weiss *et al*, 2001). The association of previously neutral stimuli paired with precipitated opioid withdrawal (conditioned withdrawal) also depends critically on the basolateral amygdala (Schulteis *et al*, 2000), and such stimuli may have motivational significance (Kenny *et al*, 2006). Neurocircuitry changes associated with drug- and cue-induced reinstatement after

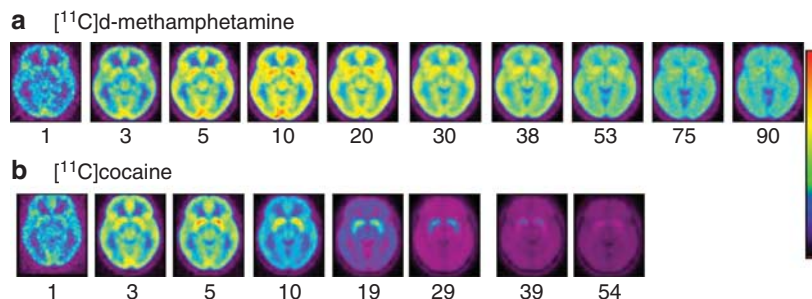
extinction have been linked to a glutamatergic pathway from the prefrontal cortex to the nucleus accumbens core, the dopamine projection from the VTA to the medial prefrontal cortex, and the GABA projection from the nucleus accumbens to the ventral pallidum (Kalivas and O'Brien, 2008).

In contrast, stress-induced reinstatement of drug-related responding in animal models appears to depend on the activation of both CRF and norepinephrine in elements of the extended amygdala (both the CeA and BNST; for reviews, see Shaham *et al*, 2003; Shalev *et al*, 2002). Protracted abstinence, largely described in alcohol dependence models, appears to involve overactive glutamatergic and CRF systems, presumably in the extended amygdala, although to a large extent this remains to be explored (de Witte *et al*, 2005; Valdez *et al*, 2002).

Human subjects with cocaine addiction show impaired performance in tasks involving attention, cognitive flexibility, and delayed reward discounting that are mediated by the medial and orbital prefrontal cortices, as well as spatial, verbal, and recognition memory impairments that are mediated by the hippocampus, and these deficits can predict poor treatment outcomes (Aharonovich *et al*, 2006; Bolla *et al*, 2003). Parallel animal studies of the orbitofrontal, prefrontal cortex, and hippocampus in addiction using animal models have begun to show some of the deficits reflected in human studies. Experimenter-administered cocaine produced impairments in reversal learning (an orbital frontal task) in rats and monkeys (Jentsch *et al*, 2002; Schoenbaum *et al*, 2004; Calu *et al*, 2007). Perhaps even more compelling, animals allowed extended access, but not limited access, to cocaine showed deficits in working memory (a prefrontal-cortex-dependent task), sustained attention task (a prefrontal-cortex-dependent task), and an object recognition task (a hippocampus-dependent task; Briand *et al*, 2008a, b; George *et al*, 2008). In one study (Briand *et al*, 2008a), these deficits were associated with a significant decrease in dopamine D<sub>2</sub> receptor mRNA in the medial and orbital prefrontal cortices, an observation also consistent with human imaging studies. Thus, animal studies using models of compulsive stimulant administration are beginning to show deficits associated with human cocaine addiction (see Human studies: imaging and neuropsychopharmacology).

### HUMAN STUDIES: IMAGING AND NEUROPSYCHOPHARMACOLOGY

As noted above, evidence from preclinical and clinical studies suggests that addiction represents sequential neuroadaptations. As a result, an initial impulsive action turns compulsive and becomes (eventually) chronic and relapsing. Work from imaging studies has provided evidence that this transition involves reprogramming of neuronal circuits that process (1) reward and motivation; (2) memory, conditioning, and habituation; (3) executive



**Figure 3.** Brain images obtained at different times after administration for [ $^{11}\text{C}$ ]d-methamphetamine and for [ $^{11}\text{C}$ ]cocaine ( $n = 19$  for each drug) showing axial planes at a level that transects the basal ganglia. Note the fast uptake of both drugs in the brain and the much slower clearance for [ $^{11}\text{C}$ ]d-methamphetamine than for [ $^{11}\text{C}$ ]cocaine (taken with permission from Fowler *et al*, 2008).

function and inhibitory control; (4) interoception and self-awareness; and (5) stress reactivity. This transition is heavily influenced by genetic, developmental, and environmental factors and their dynamic interactions, which will determine the course and severity of the addiction.

Similar to preclinical investigations, distinguishing the three stages in the recurring course of addiction in humans (intoxication, withdrawal, and craving/relapse) has been useful. The following sections describe these stages and some of the relevant neuronal circuits that underlie them.

### Binge/Intoxication Stage

Most cases of addiction are initiated by the abuse of substances that are sought because of their hedonic properties. However, drug experimentation also results from the reinforcing effects of conforming to social groups (peer pressure) with the eventual subsequent transfer of motivation to taking the drug for its reinforcing effects. Infrequently, the first use of a drug may be related to its therapeutic properties (such as opiate analgesics for pain or stimulants for attention-deficit hyperactivity disorder). As shown by preclinical studies, a key element of the reinforcing effects of drugs is broadly accepted to involve their ability to trigger large increases in extracellular dopamine in limbic regions (including the nucleus accumbens). Although acute drug self-administration is a good animal model for drug intoxication, using animal models to assess the subjective correlates of drug-induced dopamine increases is difficult. Brain imaging studies in humans have been instrumental in showing that drug-induced increases in dopamine in the striatum (including the ventral striatum where the nucleus accumbens is located) are associated with subjective descriptors of reward (eg, pleasure, high, euphoria; Volkow *et al*, 1996b). Moreover, these studies have shown that fast dopamine changes are associated with the subjective perception of reward, whereas slow and stable dopamine increases do not induce these subjective responses (Grace, 2000; Volkow and Swanson, 2003).

The pharmacokinetic properties of drugs, which influence the speed of delivery into the brain as well as the duration of their actions, are key elements of their addiction potential. Pharmacokinetic properties determine the doses, routes of

administration, and frequency of drug use within a given binge episode. For example, comparison of the brain pharmacokinetics of cocaine and of methamphetamine reveals that both reach the brain very rapidly (although cocaine is somewhat faster than methamphetamine) but that cocaine clears out of the brain much faster than methamphetamine (Figure 3). This difference helps explain why cocaine is taken every 30–60 min during a binge, whereas methamphetamine is taken every couple of hours (Fowler *et al*, 2008). The importance of pharmacokinetics also helps explain why most abused drugs (with the exception of alcohol) are injected, smoked, or snorted. These routes allow for a much faster delivery of the drug to the brain than when taken orally (Volkow *et al*, 2000). Pharmacokinetics also help explain why stimulant drugs such as methylphenidate or amphetamine, which also increase dopamine, are not typically perceived as reinforcing when taken orally as prescribed therapeutically (Chait, 1994; Volkow *et al*, 2001b).

Clinical studies have also shown that the expectation of the drug's effects significantly influences the rewarding responses to drugs, such that the behavioral as well as regional brain activation response of the brain to the drug tends to be more intense when a rewarding drug is expected compared with when the same drug is received unexpectedly (Volkow *et al*, 2003). The dependency of the drug's rewarding effects on context and expectation suggests the importance of other neurotransmitters such as glutamate, which modulates the reactivity of dopamine cells and dopamine release in the nucleus accumbens, in the rewarding effects of drugs of abuse (Kalivas and Volkow, 2005).

### Withdrawal/Negative Affect Stage

The response that follows the stage of drug intoxication differs markedly across drugs and is influenced by the chronicity and frequency of its abuse. For some drugs such as opiates, alcohol, and sedative hypnotics, drug discontinuation in chronic drug users can trigger an intense, acute physical withdrawal syndrome that, if not properly managed and when severe, can sometimes be fatal. All drugs of abuse are associated with a motivational withdrawal syndrome characterized by dysphoria, irritability, emotional

distress, and sleep disturbances that persist even after protracted withdrawal. The neurobiology of acute withdrawal is distinct from protracted or motivational withdrawal, and both contribute to relapse. Few imaging studies have been carried out during acute withdrawal. One such study that measured changes in dopamine during heroin withdrawal failed to document the dopamine decreases in the nucleus accumbens that had previously been reported with microdialysis in the rodent brain (Wang *et al*, 1997). From this study, it is unclear whether the results reflect the lack of involvement of striatal dopamine during acute withdrawal in heroin abusers or the limited sensitivity of the positron emission tomography (PET) technology.

The mechanisms underlying acute withdrawal are likely to be drug specific and reflect adaptations in the molecular targets of these drugs. For example, during the first few days of cocaine withdrawal, enhanced sensitivity of the brain to the effects of GABA-enhancing drugs occurs that may reflect the downregulation of this neurotransmitter with chronic cocaine use (Volkow *et al*, 1998). Similarly, brain imaging studies have also revealed decreases in endogenous opioids during cocaine withdrawal, which may contribute to the irritability, malaise, and dysphoria that occur during this phase of motivational withdrawal (Zubieta *et al*, 1996).

During protracted withdrawal, once the signs and symptoms of acute withdrawal have subsided, imaging studies have documented hypofunction in dopamine pathways, demonstrated by decreases in D<sub>2</sub> receptor expression and decreases in dopamine release, which may contribute to the anhedonia (ie, decreased sensitivity to rewarding stimuli) and amotivation reported by drug-addicted subjects during protracted withdrawal (Volkow *et al*, 1997b, 2007; Martinez *et al*, 2004, 2005). The decreased reactivity of dopamine to reinforcing stimuli is also present after protracted withdrawal from alcohol when acute physical withdrawal has subsided. In contrast to the decreased sensitivity to rewards (including drug rewards), imaging studies have reported that during detoxification, enhanced sensitivity to conditioned cues also occurs. Abstinence from smoking, for example, can dramatically potentiate neural responses to smoking-related cues (McClernon *et al*, 2009). These conditioned responses sustain the cycle of abstinence and relapse that characterizes substance use disorders (Childress *et al*, 1988).

In addition, imaging studies evaluating markers of brain function have shown that drug abusers tested during protracted detoxification show evidence of disrupted activity of frontal regions, including dorsolateral prefrontal regions, cingulate gyrus, and orbitofrontal cortex, which is hypothesized to underlie their impaired inhibitory control and impulsivity and contribute to relapse (see the following section for discussion).

### Preoccupation/Anticipation (Craving) Stage

The enhanced sensitivity to conditioned cues, which include emotional states, triggers the latent preoccupation/

anticipation (craving) stage, which is characterized by an increase in drug craving. Indeed, stress is a powerful trigger of relapse to drug-taking behaviors through the activation of brain circuits involved in reward processing and in the attentional and mnemonic bias for drug use reminders (Duncan *et al*, 2007). This chronic relapse phenomenon is broadly recognized as one of the most challenging problems in fighting drug addiction. Addicted subjects are liable to return to compulsive drug-taking long after experiencing acute withdrawal symptoms (Langleben *et al*, 2008). The gradual reorganization of reward and memory circuits, brought about by chronic drug abuse, is hypothesized to be crucial to the mounting of these responses. Both dopamine and glutamate have been identified in preclinical studies as contributing to the neuroplastic changes associated with conditioned responses. Moreover, plastic changes in CRF and glucocorticoid receptors likely participate in the enhanced sensitivity to stressors. In humans, the lack of suitable radiotracers to assess glutamate neurotransmission and the lack of ligands for CRF or glucocorticoid receptors have limited the studies of craving mostly to the dopamine system.

## NEUROCIRCUITRY DYNAMICS IN THE TRANSITION TO ADDICTION

The neurocircuitry outlined above forms the basis for the neuroplasticity associated with the development of addiction. Summarized below are neuroadaptive changes engaged within the circuits that represent the stages of the addiction cycle outlined above. Five circuits are hypothesized to be engaged in succession, including (1) mesolimbic dopamine system, (2) ventral striatum, (3) ventral striatum/dorsal striatum/thalamus circuits, (4) dorsolateral frontal cortex/inferior frontal cortex/hippocampus circuits, and (5) extended amygdala (Figure 4). The relative weighting and direction of these neuroadaptive changes is illustrated in the circuit diagram of the addicted state (Figure 5).

### Mesolimbic Dopamine System: Incentive Salience Pathways, Salience Attribution

One major hypothesis guiding the neuroplasticity associated with addiction is focused on the mesolimbic dopamine system. The hypothesis is that drugs of abuse, particularly cocaine and amphetamine, increase dopamine release in a more prolonged and unregulated manner than natural stimuli, resulting in changes in synaptic plasticity both within the dopamine system and in dopamine-receptive neurons (Wolf, 2002). These changes ultimately usurp normal learning mechanisms to shift neurocircuitry to associations or a form of habit-learning that persists in the face of significant adverse consequences (a component of compulsivity; Everitt and Wolf, 2002; Hyman *et al*, 2006).

Animal models of behavioral sensitization have focused largely on the increased locomotor-activating effects of psychomotor stimulant drugs in animals with a history of







neurotransmission only in rats that showed behavioral sensitization (Pierce *et al*, 1996). In addition, cocaine-sensitized mice showed an enhancement of LTP in nucleus accumbens slices during withdrawal, presumably reflecting increased activity of glutamatergic activity (Yao *et al*, 2004). An increased surface-to-intracellular ratio of glutamate-1 receptors (GluR1) has been observed 21 days after the last injection of cocaine, suggesting a slowly developing redistribution of AMPA receptors to the surface of nucleus accumbens neurons, particularly in those lacking GluR2 (Boudreau and Wolf, 2005; Conrad *et al*, 2008). The increases in cell-surface AMPA receptors depends on activation of dopamine D<sub>1</sub> receptors and subsequent protein kinase A signaling (Chao *et al*, 2002). Functionally, overexpression of GluR1 in the nucleus accumbens facilitated extinction of cocaine-seeking responses (Sutton *et al*, 2003) and increased brain stimulation reward thresholds, reflecting decreased reward and possibly decreased motivated behavior (Todtenkopf *et al*, 2006). However, a single reexposure to cocaine during extended withdrawal produced synaptic depression, which may reflect the enhanced glutamate release during cocaine reexposure (Kourrich *et al*, 2007). Curiously, the increase in AMPA receptor expression observed with cocaine does not occur in amphetamine-sensitized rats, leading to the hypothesis of different functional effects of glutamate projections to the nucleus accumbens during cocaine *vs* amphetamine withdrawal (Nelson *et al*, 2009).

Consistent with the results of altered glutamate neurotransmission in cocaine-sensitized rats, microdialysis and microinjection studies have shown that following chronic cocaine, decreased basal release of glutamate occurs but sensitized synaptic glutamate release during reinstatement of extinguished drug-seeking in rats (Kalivas and O'Brien, 2008; McFarland *et al*, 2003). This glutamate dysregulation has been hypothesized to be caused by decreased function of the cystine–glutamate exchanger (Baker *et al*, 2003) and desensitization of the metabotropic glutamate mGlu2/3 receptor. Lower basal levels of glutamate, combined with increased release of synaptic glutamate from activation of prefrontal cortex afferents to the nucleus accumbens, are hypothesized to result in a drive to engage in drug-seeking (Kalivas, 2004).

These long-lasting synaptic effects produce both a decrease in glutamate neurotransmission during chronic administration of the drug and a persistent increase in the efficacy of glutamatergic synaptic neurotransmission during reinstatement following withdrawal. These dynamic changes may promote cellular excitation, which has been hypothesized to be an important substrate for sensitization and drug-related learning in the addictive state (Kauer and Malenka, 2007; Wolf *et al*, 2004).

As previously suggested by animal models, the magnitude of striatal dopamine release (particularly in its ventral aspect) in humans correlates positively with the hedonic response to most drugs of abuse, including amphetamine

(Drevets *et al*, 2001), cocaine (Volkow *et al*, 1997a), methylphenidate (Volkow *et al*, 2002), and nicotine (Sharma and Brody, 2009). The drug-dependent, fast, and supraphysiological increases in dopamine are likely to mimic the dopamine changes induced by the phasic dopamine cell firing that occurs in response to salient stimuli, thus categorizing the drug experience as one that is highly salient, an experiential outcome that commands attention and promotes arousal, conditioned learning, and motivation (Volkow *et al*, 2004b). On the basis of findings in laboratory animals, the frequent exposure to these drug responses in drug abusers is postulated to result in the recalibration of dopamine-activating (reward) thresholds for natural reinforcers.

Thus, one can envision the development of a change in firing in mesolimbic dopamine neurons that begins with one administration of the drug, develops into LTP first in the VTA then nucleus accumbens, and via feedback loops subsequently engages the dorsal striatum. Moreover, long-term changes in the CeA and medial prefrontal cortex may follow, and combined with dysregulation of the brain stress systems (see below) may provide a powerful drive for drug-seeking behavior even months after drug withdrawal (Figure 4 and 5).

### Ventral Striatum/Dorsal Striatum/Thalamus: Voluntary to Habitual Drug-Seeking

The hypothesis that dorsal striatal circuitry has a key role in the development of habitual compulsive cocaine use is supported by data showing the importance for the dorsal striatum in stimulus–response habit learning (Yin *et al*, 2005) and microdialysis studies showing that prolonged cocaine-seeking increased dopamine release in the dorsal striatum but not ventral striatum (Ito *et al*, 2002). Disconnection of the ventral striatum from the dorsal striatum in rats self-administering cocaine on a second-order schedule only showed a deficit in animals with well-established ‘compulsive’ intake but not in animals that recently acquired the second-order schedule (Belin and Everitt, 2008). Thus, the hypothesis is that drug addiction represents changes in associative structures to become automatic or habitual and involves a gradual engagement of dorsal striatal mechanisms.

Animal studies have strongly suggested that with repeated drug exposure neutral stimuli that are associated with the drug can eventually acquire the ability to increase dopamine by themselves. Brain imaging studies confirmed this in addicted humans (Volkow *et al*, 2008a; Heinz *et al*, 2004). These studies showed that drug-associated cues induced dopamine increases in the dorsal striatum (caudate and putamen), an effect that correlated with self-reports of craving. The fact that the magnitude of the dopamine increases triggered by the cues was associated with the degree of addiction severity highlights the importance of these conditioned dopamine responses in the process of drug addiction in humans.

Clinical studies have also shown that the striatal slow dopamine increases induced by acute administration of oral methylphenidate do not elicit craving in cocaine abusers unless they are coupled to drug-associated cues (Volkow *et al*, 2008a). This most likely reflects the fact that the craving results from fast dopamine increases achieved with phasic dopamine firing, as opposed to slow dopamine increases achieved with tonic dopamine firing and in the experiment with oral methylphenidate. In fact, intravenous administration of methylphenidate, which results in fast dopamine increases, induces intense craving.

Brain imaging studies have also shown that, in drug-addicted subjects, these processes involve the orbitofrontal cortex, a brain region implicated in salience attribution and motivation, disruption of which results in compulsivity, and is a brain region with heavy projections to the dorsal striatum. The cingulate gyrus is also involved and is a brain region implicated in inhibitory control and conflict resolution, disruption of which results in impulsivity (Volkow *et al*, 2004b). Moreover, in cocaine-addicted, but not nonaddicted, subjects, the intravenous administration of methylphenidate, which cocaine abusers report has effects similar to those of cocaine, activated the orbital and medial prefrontal cortices, and this activation was associated with cocaine craving (Volkow *et al*, 2005). Similarly, in marijuana-addicted subjects, but not in nonaddicted individuals, acute administration of  $\Delta^9$ -THC activated the orbitofrontal cortex (Volkow *et al*, 1996a). Activation of the orbitofrontal cortex and cingulate gyrus is also triggered by conditioned cues that predict reward and trigger craving (McClernon *et al*, 2009). Interestingly, these are regions that regulate dopamine cell firing and release, which have been postulated to be necessary for the enhanced incentive motivational values of drugs in addicted individuals (mirroring a hypothesis based on animal studies; Volkow *et al*, 1999). When combined, these observations strongly suggest that the dopamine increases associated with conditioned cues are not primary responses, but rather the result of feedback stimulation of dopamine cells, most likely glutamatergic afferents from the prefrontal cortex and/or amygdala. On the basis of these findings, the activation of the orbitofrontal cortex, with concomitant increases in dopamine produced by the drug, has been hypothesized to contribute to the compulsive drug consumption that characterizes drug bingeing in addicted individuals (Volkow *et al*, 2007).

Indeed, human neuroimaging studies show that the prefrontal cortex (orbitofrontal, medial prefrontal, prelimbic/cingulate) and the basolateral amygdala are critical in drug- and cue-induced craving in humans (Franklin *et al*, 2007). In prefrontal regions (eg, cingulate gyrus and orbitofrontal cortex), these changes have been associated with a reduction in striatal dopamine D<sub>2</sub> receptor availability observed in addicted subjects (Heinz *et al*, 2004; Volkow *et al*, 1993, 2001a, 2007). These associations could either reflect a disruption of frontal brain regions secondary

to changes in striatal dopamine activity, or alternatively they could reflect a primary disruption of frontal regions that regulate dopamine cell activity. Indeed, a recent PET study provided evidence that prefrontal brain regions regulate the value of rewards by modulating dopamine increases in the ventral striatum, a regulatory mechanism that becomes dysfunctional in addicted individuals (Volkow *et al*, 2007).

Thus, concomitant dopamine and glutamate neurotransmission in the dorsal striatum, a region implicated in habit learning and action initiation, is involved in cue/context-dependent craving. As such, the dorsal striatum may be a fundamental component of addiction (Volkow *et al*, 2006). Research on novel strategies to inhibit cue-conditioned dopamine and glutamate responses is a major focus of current medications development efforts.

The thalamus has not been studied as extensively in the context of addiction. However, because of its integrative function in the regulation of arousal and attentional modulation, this region has been increasingly implicated in the addiction process. For example, intravenous administration of a stimulant drug in cocaine abusers, but not in controls, increased dopamine neurotransmission in the thalamus, an effect associated with craving (Volkow *et al*, 1997a). In contrast, compared with controls, cocaine abusers show hypoactivation of the thalamus, possibly reflecting noradrenergic and/or dopaminergic deficits, when performing a cognitive task (Tomasi *et al*, 2007b). Similarly, the thalamus was reported to show attenuated activation while performing a visual cognitive task in smokers exposed to nicotine (Sharma and Brody, 2009). These results suggest that thalamic abnormalities in cocaine abusers may contribute not only to impairments in sensory processing and attention but also to craving. Interestingly, changes in dopamine transmission in the thalamus and striatum appear to be involved in the deterioration of cognitive performance (eg, visual attention and working memory) that inexorably follows a period of sleep deprivation (Volkow *et al*, 2008b). Thus, more research that builds upon the available preliminary data is warranted.

### Dorsolateral Frontal Cortex, Inferior Frontal Cortex, Hippocampus: Cognitive Control, Delayed Gratification, and Memory

Addiction also entails perturbations in cortically regulated cognitive and emotional processes, which cause the overvaluing of drug reinforcers at the expense of the undervaluing of natural reinforcers, and deficits in inhibitory control of drug responses (Goldstein and Volkow, 2002). As a result, an underperforming prefrontal system is widely believed to be crucial to the addiction process.

One of the components in such a system is impulse control, which is among the most robust cognitive risk factors for substance use disorders. Cocaine appears to have a direct effect on the neurobiology underlying impulse control. After an intravenous injection of cocaine, cocaine

users actually showed an improvement in a motor response inhibition task and concomitant increased activation in their right dorsolateral and inferior frontal cortices (Garavan *et al*, 2008). Because these areas are considered to be important in impulse control, this observation suggests that some of the acute effects of cocaine could in fact mediate a transient reversal of the chronic hypofunction in impulse control circuitry.

Another important function that resides in frontocortical areas is the ability to choose between small and immediate rewards compared to large but deferred rewards, which can be measured using a delayed discounting task. A recent study found that both the dorsolateral and inferolateral frontal cortex gray matter volumes inversely correlated with preference for immediate gratification during decision-making (Bjork *et al*, 2009). This finding suggests that abnormalities in frontocortical regions may underlie the inability to delay gratification, a trait that is characteristic of addiction and other psychiatric disorders.

The neural substrates of memory and conditioned learning are among the major circuits undergoing aberrant neuroadaptations in response to chronic drug exposure (Volkow *et al*, 2004a). Different memory systems have been proposed to be involved in drug addiction, including conditioned-incentive learning (via the nucleus accumbens and amygdala), habit learning (via the caudate and putamen), and declarative memory (via the hippocampus; White, 1996), which is the focus of this section.

Over the past decade, many provocative animal studies have suggested that addictive drugs can disrupt neurogenesis in the adult hippocampus (Canales, 2007). Damage to the ventral subiculum of the hippocampus was shown to affect cocaine self-administration in rats (Caine *et al*, 2001). Such observations have provided insights into the possible involvement of a dysregulated hippocampus in human addiction. This hypothesis is an extension of current knowledge because the hippocampus is broadly viewed as important in contextual conditioning, namely in the processing of contextual cues by which memories can be accessed and retrieved. In fact, declarative memory has been long recognized to be involved in learning and the linking of affective conditions or circumstances with drug-taking experiences. Studies with PET and functional magnetic resonance imaging have shown that cue-elicited craving, as well as acute intoxication, activates the hippocampus and amygdala (Volkow *et al*, 2004a). For example, the craving that cocaine users experience while exposed to drug-related stimuli is accompanied by blood flow increases in a distributed region implicated in several forms of memory, including the amygdala (Childress *et al*, 1999; Grant *et al*, 1996; Kilts *et al*, 2001) and hippocampus (Kilts *et al*, 2001).

Therefore, new approaches to disrupt memory reconsolidation may help erode the strong associations between context and drug (Lee, 2008; Lee *et al*, 2005). Interestingly,  $\beta$ -blockers have already shown a promising capacity to inhibit conditioned responses to both natural reinforcers

and aversive stimuli (Miranda *et al*, 2003). Moreover, results from a more recent study suggest that drug-induced conditioned responses may also be sensitive to  $\beta$ -blockade treatment (Milton *et al*, 2008). Similarly, further research on GABA-enhancing drugs also seems warranted. GABAergic stimulation, which can attenuate Pavlovian conditioning, appears to disrupt the response to drugs of abuse in animals (Volkow *et al*, 2004a) and may be a useful strategy to treat addiction in humans (Dewey *et al*, 1998).

### Extended Amygdala: Negative Reinforcement Pathways

Compulsive drug use defined by increased intake of drug with extended access is accompanied by a chronic perturbation in brain reward homeostasis using measures of brain stimulation reward thresholds. The differential exposure to drug self-administration has dramatic effects on reward thresholds that progressively increase (ie, decreased reward) in extended-access, but not in limited-access, rats across successive self-administration sessions (Ahmed *et al*, 2002; Kenny *et al*, 2006; Wee *et al*, unpublished results). Animals with extended access to cocaine are more sensitive to the blockade of self-administration by dopamine antagonists and partial agonists (Ahmed and Koob, 2004; Wee *et al*, 2007), and the opioid partial agonist buprenorphine dose dependently decreased heroin self-administration in extended-access, opioid-dependent rats (Chen *et al*, 2006b), suggesting that reversal of reward deficits can blunt the motivational drives of drug addiction. This mechanism could underlie the benefit of methadone and buprenorphine treatment in heroin addiction.

As noted above, CRF antagonists blocked the anxiogenic and aversive-like effects of drug withdrawal, and withdrawal from all drugs of abuse activated CRF in the CeA. These observations led to the hypothesis that activation of CRF, specifically extrahypothalamic CRF in the CeA, contributed to the motivational state driving compulsivity from the negative reinforcement perspective (Koob and Le Moal, 2008). Thus, one would predict that blockade of the brain stress systems in animal models of extended access to drugs may block the motivation for excessive drug intake. CRF antagonists selectively blocked the increased self-administration of drugs associated with extended access to intravenous self-administration of cocaine, nicotine (Koob, 2008), heroin (Greenwell *et al*, 2009), and alcohol (Koob, 2008). A particularly dramatic example of the motivational effects of CRF in the extended amygdala in dependence can be observed in animal models of ethanol self-administration in dependent animals in which a CRF<sub>1/2</sub> peptide antagonist injected into the amygdala blocked the increase in ethanol self-administration during withdrawal (Funk *et al*, 2006; Koob, 2008).

Although less well developed, evidence suggests involvement of norepinephrine systems in the extended amygdala in the negative motivational state and increased self-administration associated with dependence (Koob, 2009b). Consistent with the



role of the dynorphin- $\kappa$  opioid system in the aversive effects of drug withdrawal, a  $\kappa$ -opioid antagonist blocked the excessive drinking associated with ethanol withdrawal in dependent rats and selectively blocked the increased progressive-ratio performance in rats with extended access to cocaine (Koob, 2009b; Wee *et al*, 2009).

Neuropeptide Y has dramatic anxiolytic-like properties localized to the amygdala and has been hypothesized to have effects opposite to CRF in the negative motivational state of withdrawal from drugs of abuse (Heilig *et al*, 1994; Heilig and Koob, 2007). NPY administered intracerebroventricularly blocked the increased drug intake associated with ethanol dependence (Thorsell *et al*, 2005a, b). Injection of NPY into the CeA (Gilpin *et al*, 2008) and viral vector-enhanced expression of NPY in the CeA also blocked the increased drug intake associated with ethanol dependence (Thorsell *et al*, 2007).

Thus, the CRF increases in the CeA that occur with acute withdrawal from drugs have motivational significance not only for the anxiety/aversive-like effects of acute withdrawal but also for the increased drug intake associated with dependence. Acute withdrawal also may increase the release of norepinephrine in the BNST and dynorphin in the nucleus accumbens, both of which may contribute to the negative emotional state associated with dependence. Decreased activity of NPY in the CeA also may contribute to the anxiety-like state associated with ethanol dependence. Activation of brain stress systems (CRF, norepinephrine, dynorphin), combined with inactivation of brain antistress systems (NPY) in the extended amygdala may elicit powerful emotional dysregulation with motivational significance to addiction. A number of other neurotransmitter systems have been hypothesized to modulate the extended amygdala both from the stress-induction domain (vasopressin, substance P, orexin) and the antistress domain (nociceptin, endocannabinoids; for review, see Koob, 2008). Such dysregulation may be a significant contribution to the between-system opponent processes that help maintain dependence and also sets the stage for more prolonged state changes in emotionality such as protracted abstinence.

Research on negative reinforcement mechanisms in human addiction has been very limited. With cocaine, for example, the amygdala and lateral orbitofrontal cortex were shown to be activated by unexpected but not expected cocaine infusions in active cocaine abusers (Kufahl *et al*, 2008), but cocaine abstinence was associated with large reductions in the activity of dopamine projection regions, including the amygdala (Tomas *et al*, 2007a). In apparent contrast, smoking abstinence was associated with increased cerebral blood flow in the extended amygdala, among other regions (Wang *et al*, 2007), whereas a nasal nicotine spray reduced regional cerebral blood flow in the right amygdala and left anterior temporal cortex of habitual smokers subjected to 12 h of smoking deprivation (Zubieta *et al*, 2001).

The amygdala may be equally important for processing positive reward (Murray, 2007) and reward expectancy (Holland and Gallagher, 2004), similar to processing

negative reward. Particularly interesting in the context of brain imaging research will be to understand the function of the amygdala in generating the anxiety and negative emotion frequently seen during abstinence.

A recent report highlighted the importance in addiction of the interoceptive circuit that most likely interfaces with the extended amygdala and ventral striatum. The study showed that smokers with damage to their insula (but not smokers with extrainsular lesions) were able to stop smoking easily and without experiencing either cravings or relapse (Naqvi *et al*, 2007). The insula, particularly its more anterior regions, is reciprocally connected to several limbic regions (eg, ventromedial prefrontal cortex, amygdala, and ventral striatum) and appears to have an interoceptive function, integrating the autonomic and visceral information with emotion and motivation and providing conscious awareness of these urges (Naqvi and Bechara, 2009). Indeed, brain lesion studies suggest that the ventromedial prefrontal cortex and insula are necessary components of the distributed circuits that support emotional decision-making (Clark *et al*, 2008). Consistent with this hypothesis, many imaging studies show differential activation in the insula during craving (Naqvi and Bechara, 2009). The reactivity of this brain region has been suggested to serve as a biomarker to help predict relapse.

## MOLECULAR TARGETS FOR NEUROPLASTICITY: BINGE/INTOXICATION, WITHDRAWAL/NEGATIVE AFFECT, AND PREOCCUPATION/ANTICIPATION (CRAVING)

The focus of the present review is on the neurocircuitry of addiction. However, parallel to the neuroplasticity of the neurocircuitry are the molecular changes that occur in these same structures. Chronic exposure to opiates and cocaine leads to activation of cyclic adenosine monophosphate response-element binding protein (CREB) in the nucleus accumbens and CeA (Shaw-Lutchman *et al*, 2002; Edwards *et al*, 2007). CREB can be phosphorylated by protein kinase A and by protein kinase regulated by growth factors, putting it at a point of convergence for several intracellular messenger pathways that can regulate gene expression. Activation of CREB in the nucleus accumbens with psychostimulant drugs is linked to the motivational symptoms of psychostimulant withdrawal, such as dysphoria, possibly through induction of the opioid peptide dynorphin, which binds to  $\kappa$ -opioid receptors and has been hypothesized to represent a mechanism of motivational tolerance and dependence (Nestler, 2005). Repeated CREB activation promotes dynorphin expression in the nucleus accumbens, which in turn decreases dopaminergic activity, both of which can contribute to negative emotional states. Extracellular signal-regulated kinase is another key element of intracellular signaling considered a key component in the plasticity associated with repeated administration of cocaine, specifically behavioral sensitization, cocaine reward,



and time-dependent increases in cocaine-seeking after withdrawal (ie, incubation effect; Lu *et al*, 2006; Li *et al*, 2008).

Another molecular target for regulating the plasticity that leads to addiction is dysregulation of cystine–glutamate exchange, which is hypothesized to promote pathological glutamate signaling related to several components of the addiction cycle. Here, repeated administration of cocaine blunts cystine–glutamate exchange, leading to reduced basal and increased cocaine-induced glutamate in the nucleus accumbens that persists for at least 3 weeks after the last cocaine treatment (Baker *et al*, 2003). Most compelling is the observation that treatment with *N*-acetylcysteine, by activating cystine–glutamate exchange, prevented cocaine-induced escalation and behavioral sensitization, restored the ability to induce LTP and long-term depression in the nucleus accumbens, and blunted reinstatement in animals and conditioned reactivity to drug cues in humans (Moussawi *et al*, 2009; LaRowe *et al*, 2007; Madayag *et al*, 2007).

CREB and other intracellular messengers can activate transcription factors, which can change gene expression and produce long-term changes in protein expression, and, as a result, neuronal function. Although acute administration of drugs of abuse can cause a rapid (within hours) activation of members of the Fos protein family, such as *c-fos*, FosB, Fra-1, and Fra-2 in the nucleus accumbens, other transcription factors, isoforms of  $\Delta$ FosB, a highly stable form of FosB, have been shown to accumulate over longer periods of time (days) with repeated drug administration (Nestler, 2005). Animals with activated  $\Delta$ FosB have exaggerated sensitivity to the rewarding effects of drugs of abuse, and  $\Delta$ FosB may be a sustained molecular ‘switch’ that helps to initiate and maintain a state of addiction (McClung *et al*, 2004). Whether (and how) such transcription factors influence the function of the brain stress systems, such as CRF and those described above, remains to be determined.

## SUMMARY AND CONCLUSIONS

In summary, multiple brain regions and circuits are disrupted in drug addiction and are likely to contribute differentially to the complex phenotype observed in addicted individuals (Figure 5). Although some of these functional abnormalities may be present to a greater or lesser extent across all classes of drug addictions, some of the changes may be specific to certain types of drugs. For example, long-lasting decrements in the DAT in the striatum are observed in methamphetamine but not in alcohol or cocaine addictions. Conversely, decrements in dopamine D<sub>2</sub> receptors in the striatum are observed in subjects addicted to all of the drugs of abuse that have been investigated, and increased activation of brain stress systems such as CRF has been observed in animal models during acute withdrawal for all types of drugs. Importantly, the neuronal abnormalities that become manifest in an

addicted individual and that can be uncovered by imaging and/or neuropsychopharmacological studies are a reflection of not only a given chronic drug exposure trajectory, but also an individual’s specific constellations of genetic, developmental, and environmental characteristics.

## FUTURE RESEARCH DIRECTIONS

The advances outlined above point the way to future directions for research in the neurocircuitry of addiction in the same conceptual framework of binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. The rich resources of modern neurosciences applied to the neurobiology of addiction offer an opportunity to not only understand the neurocircuitry of the addiction process but also to provide the keys to understanding vulnerability and providing treatment for this devastating disease.

In the binge/intoxication stage of the addiction cycle, how neuroplasticity that begins with a change in firing in mesolimbic dopamine neurons during initial drug exposure is translated to engagement of the dorsal striatum, disruption of frontal system function, and recruitment of brain stress systems and results in a residual powerful drive for drug-seeking behavior even months after withdrawal remains to be determined. For example, what is the relationship between vulnerability to impulsivity and subsequent compulsivity in the neuroplasticity of the circuits described above? Such future studies may involve molecular genetic approaches that range from selective breeding to upregulation or knockdown of molecular mechanisms within specific brain circuits using short-hairpin RNA technology.

In the withdrawal/negative affect stage, engagement of the brain stress systems, such as CRF, in animal models needs to be extended to other interactive brain stress systems and explored in human studies. Numerous other neurotransmitter systems that interact with the brain stress system are only now being explored, such as dynorphin, NPY, substance P, nociceptin, and orexin. Virtually unexplored at this stage are human imaging studies of this component of the addiction cycle and human imaging of brain neurotransmitter systems implicated in motivational aspects of drug withdrawal. The development of novel radioactive ligands for human imaging studies that bind to the receptors of the above neurotransmitter systems would be a great boost to the field.

In the preoccupation/anticipation stage, human neuroimaging studies show that the prefrontal cortex (orbitofrontal, medial prefrontal, prelimbic/cingulate) and the basolateral amygdala are critical in drug- and cue-induced craving. Whether such associations reflect a disruption of frontal brain regions secondary to changes in striatal dopamine activity, or alternatively reflect a primary disruption of frontal regions that regulate dopamine cell activity, remains to be determined. New approaches to the study of memory reconsolidation may help elucidate the

strong associations between context and drug. The importance in addiction of the interoceptive circuit involving the insula and other regions that most likely interface with the extended amygdala and ventral striatum remains to be determined. The reactivity of these brain circuits may serve as a biomarker to help predict relapse and help predict treatment efficacy. Human post-mortem studies, human laboratory studies, and neurocircuitry studies in parallel animal models will likely yield promising results in this domain.

Finally, molecular and genetic changes that convey the changes in activity of the neurocircuits in all three stages of the addiction cycle described above are only now being elucidated. Changes in transmitter regulatory systems, transcription factors, and even gene regulation at the epigenetic level may explain how circuits are dysregulated, stay dysregulated, and provide vulnerability to dysregulation initially or long into abstinence. Ultimately, neurobiological targets elucidated through the framework of the neurocircuitry of addiction will provide targets for identifying genetic vulnerability in the human population, and genetic vulnerability in the human studies may identify novel targets to be explored at the mechanistic level in animal studies.

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## DISCLOSURE

The authors declare no conflicts of interest.

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