Drug addiction is a chronic relapsing disorder for which research has been dedicated to understand the various factors that contribute to development, loss of control, and persistence of compulsive addictive behaviors. In this review, we provide a broad overview of various theories of addiction, drugs of abuse, and the neurobiology involved across the addiction cycle. Specific focus is devoted to the role of the mesolimbic pathway in acute drug reinforcement and occasional drug use, the mesocortical pathway and associated areas (e.g., the dorsal striatum) in escalation/dependence, and the involvement of these pathways and associated circuits in mediating conditioned responses, drug craving, and loss of behavioral control thought to underlie withdrawal and relapse. With a better understanding of the neurobiological factors that underlie drug addiction, continued preclinical and clinical research will aid in the development of novel therapeutic interventions that can serve as effective long-term treatment strategies for drug-dependent individuals.
development and persistence of substance abuse disorders. In this chapter, we provide a brief overview of the theory, stages, and neurocircuitry that likely underlies the development of the addiction cycle (e.g., acute reinforcement/drug use, escalation/dependence, withdrawal/relapse).

THEORIES AND STAGES OF ADDICTION

Early theories suggested that addictive behaviors develop because of the pleasurable effect initially produced by a drug, with dependence occurring as a function of a recurrent drive for reward (Wise 1980). Although positive reinforcement is initially involved in the development of a substance abuse disorder, long-term drug abuse often results in the occurrence of aversive psychological and physiological effects if the drug is withheld, resulting in continued use as a means to avoid the aversive consequences of drug withdrawal (i.e., negative reinforcement) (Cami and Farre 2003). Thus, addictive behaviors likely include a gradual shift from positive reinforcement (impulsivity) to negative reinforcement (compulsivity) (Koob 2004). Although positive and negative reinforcement play a role in the initiation and maintenance of drug addiction behaviors, respectively, and thus may account for some aspects of the persistence of drug addiction (Wilkerson 1973), these conditioning theories cannot fully explain many aspects of drug dependence, such as the resumption of drug-seeking and drug-taking behaviors following a prolonged period of abstinence (i.e., relapse) when overt withdrawal symptoms have long dissipated. As such, a number of findings indicate that prolonged drug use leads to a series of neuroadaptations, thus contributing to the enduring nature of the addictive state.

Robinson and Berridge (Robinson and Berridge 1993; Berridge and Robinson 1995) postulated in their “incentive sensitization” theory of addiction that chronic exposure to drugs of abuse results in alterations in a number of neural systems, including areas normally involved in the motivation for natural appetite rewards. As a result, the addict becomes hypersensitive to drug-associated stimuli (Clark and Overton 1998), leading to a shift from drug “liking” to “wanting,” with ensuing compulsive patterns of drug-seeking behavior. In another perspective, Koob and Le Moal (1997, 2001) hypothesized that continuous drug use leads to a shift in an individual’s hedonic set point and a state of dysregulation (including enhanced sensitivity and counteradaptation) of brain reward systems. As a result, the drug user’s allostatic processes, or the ability to maintain stability or homeostasis through change, become disrupted, leading to a loss of control over drug intake and compulsive use. Other theories, including maladaptive associative learning (Di Chiara 1999; Hyman and Malenka 2001), loss of behavioral control and decision making because of altered prefrontal cortical activity (Jentsch and Taylor 1999; Franklin et al. 2002; Goldstein and Volkow 2002), and aberrant stimulus response learning resulting in the formation of engrained drug habits (Wise 2002; Everitt and Robbins 2005; Volkow et al. 2006), have centered on specific drug-induced neuroadaptations that may also play a role in the development and persistence of drug addiction. These theories collectively provide unique views on addiction, with overlap being noted among the different perspectives. However, given the multilayered complexity of addiction states and unique perspectives of each theory, it is not surprising that none can fully account for all aspects of the addictive cycle.

In general, drug addiction can be considered to consist of three stages: acute reinforcement/drug use, escalation/dependence, and withdrawal/relapse. However, whereas drug use does not necessarily result in the development of a drug dependence disorder (e.g., social smokers/drinkers), it should be noted that the acute reinforcing effects of many drugs of abuse have some predictive validity for the transition to later stages of the addiction cycle. Moreover, these stages cannot be considered to be exclusive, in that they interact with one another and culminate in persistent drug addiction behaviors (Koob and Le Moal 1997; Koob and Volkow 2010). Although significant advances in human neuroimaging and other techniques
have allowed researchers to further our understanding of the neural substrates that underlie addiction, this review will primarily focus on data derived from various animal models to provide a broad overview of the neurobiology thought to underlie development of the different stages of addictive behaviors.

**DRUGS OF ABUSE AND COMMON NEUROBIOLOGY OF ADDICTION**

Drugs of abuse are generally classified into different categories, including narcotics (e.g., opiates), cannabinoids (e.g., marijuana), depressants (e.g., ethanol), psychostimulants (e.g., nicotine, amphetamines, and cocaine), hallucinogens (e.g., lysergic acid diethylamide and ecstasy), and inhalants (e.g., toluene and nitrous oxide). Although all drugs of abuse have the potential to produce feelings of euphoria and relieve negative emotional states (Nesse and Berridge 1997), their behavioral and neuropharmacological properties are highly diverse. However, when one considers the mechanism for their acute reinforcing effects, most researchers have focused their attention on the mesocorticolimbic DA pathway (Wise 1980). This system, which mediates the rewarding effects of both natural stimuli (e.g., food, drink, and sex) and drugs of abuse, consists of dopamine (DA) cell bodies in the ventral tegmental area (VTA) that project to various limbic (i.e., the mesolimbic pathway, including the nucleus accumbens (NAcc), ventral pallidum, amygdala, hippocampus, and the bed nucleus of the stria terminalis [BNST]) and cortical structures (i.e., the mesocortical pathway, including the prefrontal cortex [PFC], orbitofrontal cortex [OFC], and the anterior cingulate). Various drugs of abuse interact with this circuit at different levels (Cami and Farre 2003) and other neurotransmitter/neuromodulator systems, including opioid peptides, GABA, glutamate, and endocannabinoids play a role in the reinforcing effects of drugs of abuse (especially nonpsychostimulants). Moreover, whereas these circuits operate in parallel, evidence suggest that they have somewhat different roles in addiction (Cami and Farre 2003). Within the mesolimbic pathway, data suggests that the NAcc (Di Chiara 2002) and ventral pallidum are involved in the primary reinforcing effects of drugs of abuse (Volkow et al. 2003). On the other hand, the amygdala (specifically the basolateral amygdala [BLA] [See 2005]) and hippocampus (both the dorsal [Fuchs et al. 2005; Meyers et al. 2006; Atkins et al. 2008] and ventral [Rogers and See 2007; Lasseter et al. 2010b]) subregions play a key role in discrete and/or contextual drug-associated learning. Within the mesocortical pathway, the PFC, OFC and anterior cingulate are involved in the regulation of emotional responses, cognitive control and executive function (Volkow et al. 1993), with long term drug use resulting in cellular adaptations in the prefrontal-NAcc glutamatergic pathway leading to persistent addictive behaviors, including the devaluation of natural rewards, diminished cognitive control, and hyper-responsiveness to drug-associated stimuli (Koob and Le Moal 2001; Kalivas and Volkow 2005). With respect to the stages of addiction outlined above, these data collectively suggest that the mesolimbic pathway (especially the VTA and NAcc) is involved in acute drug reinforcement and occasional drug use, the mesocortical pathway and associated areas (e.g., the dorsal striatum) are involved in escalation/dependence, whereas both pathways and associated areas are involved in mediating conditioned responses, drug craving, and loss of behavioral control thought to underlie withdrawal and relapse.

**NEUROCIRCUITRY INVOLVED IN ACUTE REINFORCEMENT/DRUG USE**

In general, predominant addiction theories suggest that the acute reinforcement produced by drugs of abuse involves direct or indirect enhancement of DA in the NAcc (Di Chiara and Imperato 1988; Koob and Bloom 1988). Interestingly, this system is similarly involved in the motivation and drive for natural reinforcers (Wise 2002); however, drugs of abuse produce more robust increases in accumbal DA that, unlike natural reinforcers, does not undergo adaptive change (i.e., habituation) with repeated experiences (Di Chiara 1999). These data suggest...
that the initiation of the addiction cycle not only involves drugs of abuse “hijacking” a system normally involved in the reward and reinforcement of naturally appetitive stimuli (Robbins and Everitt 1996), but this effect is persistent, adding to the consolidation of responses to drug-associated stimuli (Berke and Hyman 2000) and further promoting the repeated use of the addictive substance.

Much of our understanding of the neurobiology of the acute rewarding effects of drugs of abuse can be traced to the discovery of a brain reward system by Olds and Milner (1954). Using intracranial self-stimulation, they showed that animals would administer low levels of electrical current into a number of areas, the most sensitive of which involved the medial forebrain bundle projecting from the VTA to the basal forebrain (Olds and Milner 1954). Using this model, it has been shown that acute administration of drugs of abuse results in decreased brain stimulation reward thresholds (i.e., increased reward), with more addictive drugs producing greater reductions in thresholds (Kornetsky et al. 1979; Kornetsky and Bain 1990).

Further evidence implicating the role of DA and the mesolimbic pathway in acute drug reinforcement includes a number of studies using drug self-administration, which involves an animal performing an operant behavior (e.g., lever press) to receive a drug reinforcer. Using this model, it has been shown that systemic administration of DA synthesis inhibitors (Pickens et al. 1968; Wilson and Schuster 1974) or DA antagonists (Yokel and Wise 1975; Woolverton 1986; Corrigall and Coen 1991; Rassnick et al. 1992; Richardson et al. 1994) decreases self-administration of a variety of drugs of abuse, including psychostimulants, opiates, nicotine, and ethanol. Moreover, excitotoxic lesions of the NAcc block cocaine, heroin (Zito et al. 1985), and morphine self-administration (Dworkin et al. 1988b), with similar effects showed using 6-hydroxydopamine (6-OHDA) to selectively lesion DA pathways in the NAcc (Roberts et al. 1977, 1980; Lyness et al. 1979; Corrigall et al. 1992) or VTA (Roberts and Koob 1982). In addition, in vivo microdialysis studies have shown increases in extracellular DA in the NAcc during psychostimulant (Hurd et al. 1989; Pettit and Justice 1989; Weiss et al. 1992; Di Ciano et al. 1995; Meil et al. 1995; Pontieri et al. 1995, 1996; Wise et al. 1995b) and opiate (Hemby et al. 1995; Pontieri et al. 1995; Wise et al. 1995a) self-administration. Similar effects occur during the self-administration of a variety of other drugs of abuse, including nicotine (Pontieri et al. 1996; Lecca et al. 2006b), cannabionoids (Fadda et al. 2006; Lecca et al. 2006a), and ethanol (Weiss et al. 1993; Melendez et al. 2002; van Erp and Miczek 2007). Finally, a number of studies have shown that animals will reliably self-administer intracranial microinjections of various drugs of abuse (Myers 1974; Bozarth 1987), further supporting the role of the mesolimbic pathway in addiction. For example, animals will reliably self-administer psychostimulants, opiates, and ethanol into the NAcc (Monaco et al. 1981; Olds 1982; Hoebel et al. 1983; Chevrette et al. 2002; Rodd-Henricks et al. 2002) or VTA (van Ree and de Wied 1980; Bozarth and Wise 1981, 1982; Gatto et al. 1994; Rodd et al. 2004a,b, 2005). Moreover, these effects appear relatively selective, in that switching the response contingency, replacing the drug with artificial cerebrospinal fluid, or examination of other non-associative brain regions eliminates or prevents these behaviors.

Despite abundant evidence for its role in psychostimulant reward, there has been some debate regarding the necessity of the mesolimbic DA system for the acute reinforcing effects of other drugs of abuse (Koob 1992; Nestler 2005). In one example, 6-OHDA lesions of the NAcc, which reliably impair psychostimulant administration, generally fail to alter the self-administration of opiates (Ettenberg et al. 1982; Pettit et al. 1984; Smith et al. 1985; Dworkin et al. 1988a) or ethanol (Lyness and Smith 1992; Rassnick et al. 1993). Similar effects have also been reported for DA antagonists on opiate self-administration (Ettenberg et al. 1982; Gerrits et al. 1994), collectively suggesting that nonpsychostimulant drugs of abuse may additionally involve DA-independent mechanisms of reinforcement. In support of this hypothesis, systemic or intracranial administration of opioid
antagonists attenuate heroin (Bozarth and Wise 1983; Corrigall and Vaccarino 1988) and ethanol (Altschuler et al. 1980; Samson and Doyle 1985) self-administration. The endogenous cannabinoid system may also be involved in mediating opiate and ethanol reinforcement, in that genetic knockout (Ledent et al. 1999; Cossu et al. 2001; Hungund et al. 2003; Thanos et al. 2005) or antagonism of CB1 receptors (Caille and Parsons 2003; Colombo et al. 2005) can reduce opiate or ethanol intake. Interestingly, this effect appears specific to nonpsychostimulants, in that genetic deletion of CB1 receptors had no effect on cocaine, amphetamine, or nicotine self-administration (Cossu et al. 2001), but see Soria et al. (2005).

The collective evidence supports the notion that whereas opiate and ethanol reinforcement involves mesolimbic DA activity (Johnson and North 1992; Weiss et al. 1993), both DA-dependent and -independent mechanisms exist (Van Ree et al. 1999). Thus, although other neurotransmitter/neuromodulator systems are significantly involved in the acute reinforcing effects of numerous drugs of abuse (Koob and Le Moal 2006), the weight of evidence suggests that the mesolimbic DA system is critically involved in the reinforcing properties of drugs and, as such, the initiation of the addiction cycle. However, DA may play a differential role in chronic addictive states via alterations in mediating the reinforcing effects of drug (i.e., “liking”) to the persistence of addictive behaviors in drug dependence (i.e., “wanting”) (Berridge 2007).

NEUROCIRCUITRY INVOLVED IN DRUG DEPENDENCE

In addition to the role of DA in mediating the acute reinforcement of drugs during occasional/controlled drug use, DA activity in the mesocorticolimbic system may further promote continued, persistent drug-seeking behaviors by enhancing learning about the associations between actions and discrete, environmental, or contextual stimuli involved in the drug-taking process (Everitt et al. 2001). With repeated drug taking (i.e., as the state of drug dependence develops), these drug-associated stimuli eventually begin to dominate the behavioral output independent of goal-directed action (Everitt and Robbins 2005). These conditioned drug associations can be considered to be a form of maladaptive learning that eventually acquires an increasing role in mediating drug seeking behavior. Interactions between Pavlovian and instrumental learning processes (Everitt et al. 2001) can lead to a shift from “stimulus-reward” to “stimulus-response” learning that underlies the habitual drug seeking characteristic of chronic drug dependence. As such, this loss of controlled drug-seeking and drug-taking behavior, which is the hallmark of clinical drug addiction/dependence, has become increasingly of interest for preclinical researchers (Wolffgramm and Heyne 1995; Deroche-Gamonet et al. 2004; Vanderschuren and Everitt 2004).

The concept of drug addiction as a maladaptive and persistent habit comes from several sources, with abundant data suggesting a transition at the neuronal level from the ventral to the dorsal striatum, likely involving a progressive recruitment by spiraling DA circuitry connections within the midbrain (Haber et al. 2000; Ikemoto 2007). In contrast to the ventral striatum (i.e., the NAcc), the dorsal striatum (especially the lateral regions) appears to have little, if any, role in the acute reinforcing effects of drugs of abuse but does appear to be engaged during the development of compulsive drug seeking (Everitt et al. 2008). For example, 6-OHDA (Roberts 1992) or excitotoxic (Gabriele and See 2011) lesions of the dorsal striatum do not have any effect on cocaine self-administration. When a selective lesion of the NAcc core was paired with an infusion of the DA receptor antagonist, α-flupenthixol, into the contralateral dorsal striatum, no effect was observed in animals immediately after acquisition. However, this procedure resulted in attenuated cocaine seeking once stable responding was achieved on a second order schedule of reinforcement (Belin and Everitt 2008). In rhesus monkeys, Porrino and colleagues showed progressively greater activation of the dorsal and lateral regions of the striatum as assessed by 2-deoxyglucose autoradiography following 100, but not 5, days of cocaine self-administration (Porrino et al. 2004).
Similar data in primates showed progressive ventral-to-dorsal changes in DA transporter (Letchworth et al. 2001) and receptor (Nader et al. 2002) expression following long-term cocaine self-administration. Furthermore, microdialysis data in rats have indicated that contingent presentation of a cocaine-paired stimulus on a second order schedule of reinforcement increases extracellular DA levels in the dorsal striatum, but not NAcc, following chronic cocaine self-administration (Ito et al. 2000, 2002). Using a similar second order model, administration of α-flupenthixol into the dorsolateral striatum blocked responding for a cocaine-associated cue; however, treatment in the NAcc was without effect (Di Ciano and Everitt 2004b; Vanderschuren et al. 2005). A similar anatomical dissociation has been noted using GABA agonist inhibition in a contextual model of cocaine seeking, in which inactivation of the dorsolateral striatum (Fuchs et al. 2006a; See et al. 2007), but not the NAcc (See et al. 2007), following abstinence from chronic cocaine self-administration resulted in decreased cocaine seeking. Finally, a recent report showed that not only did extensive training on a cocaine-seeking schedule lead to a transition from goal-directed to habitual behavior (as measured by a failure to devalue the drug-taking response by contingency degradation through extinction), but also that transient inactivation of the dorsolateral striatum reduced cocaine seeking only when the drug-taking response had been devalued (Zapata et al. 2010). Combined with clinical data indicating that elevations of DA in the dorsal, but not ventral, striatum positively correlate with cue-induced craving in cocaine-dependent patients (Volkow et al. 2006; Wong et al. 2006), these data collectively suggest that the dorsal striatum becomes progressively involved in mediating drug seeking during the transition from initial voluntary use to the habitual, loss of control behavior characteristic of chronic drug addiction and dependence.

In addition to the dorsal striatum, an abundance of evidence suggests that prefrontal cortical areas may also play a role in mediating compulsive drug-seeking behavior, likely involving a loss of behavioral control and inhibition. Although habitual behaviors primarily involve cortico-striatal-thalamic circuitry (Jog et al. 1999; Canales 2005), these behaviors rely on higher level cortical processing of new information to determine if the behavior needs to be modified according to its adaptive function. As such, if the behavior becomes maladaptive, information of this unfavorable outcome from the PFC should lead to a modification or cessation of the behavior. However, despite a number of negative consequences, drug taking continues in drug-dependent individuals. Interestingly, a number of studies have shown decreased gray matter density and reduced baseline blood glucose metabolism in frontal cortical areas, including the anterior cingulate and OFC, of chronic drug users (London et al. 1999; Volkow and Fowler 2000; Franklin et al. 2002; Matochik et al. 2003; Thompson et al. 2004; Ersche et al. 2011).

Chronic cocaine abusers exhibit deficits in inhibitory control and decision-making processes (Bolla et al. 2003; Hester and Garavan 2004). In animal models, lesions of the medial PFC (mPFC), including the prelimbic and infralimbic cortex, result in enhanced acquisition of cocaine self-administration and increased responding for cocaine on a second order schedule of reinforcement (Weissenborn et al. 1997). These effects do not appear to be caused by an alteration in reinforcement (Burns et al. 1993), but rather a loss in behavior/inhibition processes (Dalley et al. 2004). Furthermore, reversible inactivation of the infralimbic cortex in rodents leads to reinstatement of extinguished cocaine seeking (Peters et al. 2008). In addition, there is an abundance of preclinical data to suggest that OFC dysfunction is significantly involved in addiction behaviors (Schoenbaum et al. 2006; Everitt et al. 2007; Olausson et al. 2007; Lucantonio et al. 2012). Similar decision-making problems have been shown for patients with OFC damage (Rogers et al. 1999), suggesting that chronic drug taking may be a casual factor for PFC-dependent deficiencies. In contrast, preexisting deficits in prefrontal cortical function (Volkow and Fowler 2000; Kaufman et al. 2003; Hester and Garavan 2004) may have led to poor decision capacities contributing to the
development of the addiction. However, a number of experimental studies in rodents and non-human primates support the view that these deficits are likely a consequence of chronic drug use history (Jentsch and Taylor 1999; Schoenbaum et al. 2006). In animals withdrawn from chronic drug exposure, psychostimulants had a profound effect on dendritic morphology (e.g., dendritic length and spine density) in the OFC and PFC (Kolb et al. 2004; Crombag et al. 2005), as well as increases in the transcription factor ΔFosB during early withdrawal from chronic cocaine (Winstanley et al. 2007). Similar drug exposure paradigms (including self-administration models) have shown evidence for cognitive inflexibility and impulsive behaviors that are relevant to addiction in humans. These include cognitive deficits on various learning tasks, such as reversal learning—deficits associated with damage to the OFC (Calu et al. 2007; Izquierdo et al. 2010; Porter et al. 2011) and extradimensional shifting—deficits associated with damage to the medial PFC (Parsegian et al. 2011), as well as enhanced impulsivity (Roesch et al. 2007; Simon et al. 2007). Taken together, these data suggest that impairments in prefrontal cortical areas following prolonged drug use may lead to the persistence of addiction behaviors by producing deficits in adaptive decision-making and behavioral control. However, these areas also likely contribute to drug seeking by enhancing the saliency and motivational significance of stimuli known to promote relapse in drug-dependent individuals.

NEUROBIOLOGY UNDERLYING RELAPSE

As previously mentioned, relapse to drug use following prolonged periods of abstinence constitutes one of the most significant problems for individuals with a history of drug dependence (Dackis and O’Brien 2001; Wagner and Anthony 2002). A number of factors contribute to craving and relapse, including exposure to environmental stimuli previously paired with drug use (i.e., conditioned drug cues), negative mood states or stress, and exposure to small amounts of the drug. For example, abstinent cocaine users report increases in drug craving when exposed to cocaine-associated stimuli (Childress et al. 1993), following stressful life events (Sinha et al. 1999), and in response to noncontingent cocaine doses (Jaffe et al. 1989). These trigger factors have been used in animal models of relapse to drug seeking, particularly in the extinction-reinstatement model following withdrawal from chronic drug self-administration (de Wit and Stewart 1981; Kalivas and McFarland 2003; Shaham et al. 2003). Typically, animals that previously self-administered a drug (usually paired with a discrete stimulus, such as light and/or tone) undergo extinction trials, whereby responding on the previously drug-paired lever no longer results in primary reinforcement. Exposure to the previously drug-paired cues, an environmental stressor, or non-contingent drug administration can robustly reinstate drug seeking (i.e., induce relapse) as indexed by increased responding on the previously drug-paired operandum (Shaham et al. 2003). As such, the extinction-reinstatement model has been useful for extensive exploration of the neural circuitry underlying relapse-like behaviors (Meil and See 1997; Neisewander et al. 2000; McFarland and Kalivas 2001; McFarland et al. 2004).

Using reinstatement models, a number of laboratories have contributed to our understanding of the neurocircuitry of relapse. In studies on cue-associated drug seeking, evidence suggests an important role for a number of mesocorticolimbic structures, especially the BLA and prefrontal cortical areas (including the anterior cingulate, prelimbic, and orbitofrontal cortices), via glutamatergic and DAergic interactions with the NAcc core. Consistent with neuroimaging studies demonstrating increases in metabolic activity in the amygdala in abstinent cocaine users exposed to drug-associated cues or drug-related imagery (Grant et al. 1996; Childress et al. 1999; Kilts et al. 2001, 2004; Bonson et al. 2002), reinstatement of cocaine seeking in rats exposed to discrete cocaine-associated cues positively correlates with increased Fos expression in the BLA (Kufahl et al. 2009). Moreover, permanent lesions or reversible inactivation of the BLA has a number of effects on discrete cue-induced drug seeking, including decreases in...
responding for stimuli associated with cocaine reinforcement (Whitehall et al. 1996; Meil and See 1997; Grimm and See 2000), and prevention of the acquisition (Kruzich and See 2001), consolidation (Fuchs et al. 2006b; Gabriele and See 2010), and expression (Kruzich and See 2001; Fuchs and See 2002; McLaughlin and See 2003; Rogers et al. 2008) of cocaine- or heroin-seeking behavior. A similar role for the BLA in contextual drug seeking has also been found (Fuchs et al. 2005, 2009), involving interactions with other areas implicated in cue-mediated drug seeking, including prefrontal cortical areas (Fuchs et al. 2007; Lasseter et al. 2011) and the hippocampus (Fuchs et al. 2005; Wells et al. 2011).

Presentation of stimuli associated with cocaine availability results in a significant elevation in extracellular DA in the BLA (Weiss et al. 2000). In addition to direct intra-BLA administration of DA receptor antagonists attenuating cocaine seeking on a second-order schedule of reinforcement (Di Ciano and Everitt 2004b), similar treatment has also been shown to attenuate the acquisition (Berglind et al. 2006) and expression (See et al. 2001) of discrete cue-induced reinstatement. Moreover, elevations in Fos (Neisewander et al. 2000; Ciccocioppo et al. 2001) and Fos-related antigen (Franklin and Druhan 2000) expression noted when animals are exposed to contextual or discrete cocaine-associated cues can be reversed by DA D1 receptor antagonism (Ciccocioppo et al. 2001). Other neurotransmitter systems, including glutamate (See et al. 2001; Feltenstein and See 2007) and acetylcholine (See et al. 2003), have also been shown to be involved in BLA-mediated cue-associative learning. Taken together, these results suggest that the BLA plays a prominent role in drug-cue associative learning and relapse, with different neurotransmitter systems likely mediating unique aspects of amygdalar processing of drug-paired stimuli.

Similar to the BLA, imaging studies have not only showed increases in metabolic activity in the PFC (specifically the dorsolateral regions) when drug-dependent individuals are exposed to drug-associated cues (Grant et al. 1996), but this activation was also positively correlated with craving (Maas et al. 1998; Bonson et al. 2002). In animal models, increases in reinstatement behavior and Fos protein or Arc mRNA expression noted in the dorsomedial PFC (dmPFC) when animals are exposed to discrete cocaine- (Zavala et al. 2008; Kufahl et al. 2009) or heroin-paired cues (Koya et al. 2006), as well as discriminative stimuli predicting cocaine (Ciccocioppo et al. 2001). Inactivation studies, including use of the sodium channel blockers tetrodotoxin (McLaughlin and See 2003; Fuchs et al. 2005) or lidocaine (Di Pietro et al. 2006) or the GABA_A and GABA_B agonists, muscimol and baclofen (Fuchs et al. 2005; LaLumiere and Kalivas 2008, 2009) have been shown to inhibit reinstatement of drug seeking when animals are exposed to discrete or contextual cocaine- or heroin-associated cues. Moreover, mediation of cue-associated reinstatement by the dmPFC likely involves glutamatergic innervation of the NAcc core, in that inhibition of heroin seeking following reversible inactivation of the dmPFC also prevents concomitant increases in glutamate within the NAcc core (LaLumiere and Kalivas 2008). This same study further supported this hypothesis by demonstrating that glutamate AMPA/kainate receptor antagonism in the NAcc also inhibits discrete cue-induced heroin seeking. Although studies examining the putative role of the infralimbic cortex in cue-mediated drug seeking have been mixed (see Lasseter et al. (2010a) for review), it appears that the lateral, but not medial, OFC is also involved in these types of drug-seeking behaviors, in that inactivation attenuates both discrete and contextual cue-induced cocaine seeking (Gallagher et al. 1999; Fuchs et al. 2004b; Lasseter et al. 2009).

Similar to the BLA and prefrontal cortices, a substantial amount of data suggests that the NAcc is significantly involved in cue-induced drug seeking. Exposure to discrete or contextual cocaine (Neisewander et al. 2000; Kufahl et al. 2009) or ethanol (Dayas et al. 2007) associated cues have been shown to induce Fos in the NAcc, with numerous studies demonstrating a particular role for the NAcc core, in that reversible inactivation selectively attenuates cocaine}
seeking (Di Ciano and Everitt 2004a; Fuchs et al. 2004a; Di Ciano et al. 2008). With respect to specific neurotransmitter systems, microdialysis and antagonist studies have indicted a particular role for DA and glutamate in mediating these behaviors. For example, exposure to discriminative stimuli predicting cocaine availability results in a robust elevation in DA in the NAcc (Weiss et al. 2000), with DA D1 receptor antagonism in the core, but not shell, decreasing drug seeking in animals exposure to discrete or contextual cues associated with heroin availability (Bossert et al. 2007). Direct infusion of AMPA or NMDA agonists into the NAcc results in reinstatement of cocaine seeking (Cornish et al. 1999), whereas AMPA/kainate and/or NMDA receptor antagonism has been shown to block cocaine seeking following exposure to drug-associated cues on a second-order schedule (Di Ciano and Everitt 2001; Backstrom and Hyyttia 2007). Although other neurotransmitter systems in the NAcc may play a role in mediating cue-induced drug seeking (e.g., acetylcholine [Zhou et al. 2007]), these data collectively suggest that cue-associated reinstatement relies on glutamate and DA interactions between the NAcc core, BLA, and dmPFC.

Similar to cue-induced drug seeking, a considerable amount of research suggests that prefrontal cortical areas, the NAcc (in particular the core), and the VTA are critically involved in mediating reinstatement following exposure to the previously self-administered drug (McFarland and Kalivas 2001). In addition to the ventral pallidum, inactivation of these regions has been shown to attenuate cocaine- (Grimm and See 2000; McFarland and Kalivas 2001; Capriles et al. 2003) or heroin-primed reinstatement (Rogers et al. 2008). Examination of the role of various neurotransmitter systems in mediating these behaviors suggests that DA and glutamate play a pivotal role in drug-primed relapse-like behaviors. For example, microdialysis studies have shown increases in accumbal DA and glutamate following a priming injection of cocaine (McFarland et al. 2003). Similarly, microinjections of DA or glutamate, as well as AMPA agonists, into the NAcc alone produce robust elevations in drug seeking (Cornish et al. 1999; McFarland and Kalivas 2001), with DA D1 receptor antagonism in the shell (Anderson et al. 2003) or AMPA/kainic receptor antagonists in the core (Cornish and Kalivas 2000) attenuating cocaine-primed reinstatement. Interestingly, DA or NMDA antagonism in the core were without effect, collectively suggesting divergent roles for DA and glutamate (via AMPA receptors) in the NAcc shell and core, respectively, for mediating cocaine-primed reinstatement.

With respect to prefrontal cortical areas, dmPFC inactivation can impair drug-primed heroin, cocaine, methamphetamine, and nicotine seeking (McFarland and Kalivas 2001; Capriles et al. 2003; Zavala et al. 2003; Hirani et al. 2006; Rogers et al. 2008). Moreover, direct infusions of DA, cocaine, or amphetamine into the dmPFC can elicit cocaine seeking, whereas DA D1 and D2 receptor antagonists have been shown to disrupt cocaine-primed reinstatement and conditioned place preference (McFarland and Kalivas 2001; Park et al. 2002; Sanchez et al. 2003; Sun and Rebec 2005), but see Capriles et al. (2003). The role for the dmPFC in mediating these behaviors appears to include glutaminergic inputs into the NAcc core, in that an enhancement in glutamate release and drug seeking following a cocaine- or heroin-prime are both reversed following dmPFC inactivation (McFarland et al. 2003; LaLumiere and Kalivas 2008).

As previously mentioned, stress has been shown to play a prominent role in the initiation and maintenance of substance dependence disorders (Higgins and Marlatt 1975; Russell and Mehrabian 1975; Koob and Le Moal 2001). In animals models of relapse, researchers have used a variety of techniques, including exposure to footshock (Erb et al. 1996; McFarland et al. 2004; Buffalari and See 2009) or pharmacological stressors (Lee et al. 2004; Shepard et al. 2004; Le et al. 2005; Buffalari et al. 2012), to model stress-induced relapse-like behaviors. As such, examination of the neurocircuitry involved in stress-induced reinstatement using these methods suggests both overlapping, yet distinct, neural systems mediating these behaviors relative to other forms of reinstatement (Stewart 2000; Shaham et al. 2003). Similar to
other forms of relapse, inactivation of prefrontal cortical areas, the NAcc, or the VTA has been shown to decrease stress-induced reinstatement, with a unique contribution noted for the BNST and central nucleus of the amygdala (CeA) in mediating these behaviors (Capriles et al. 2003; McFarland et al. 2004). Although it has been suggested that DA only plays a modulatory role in stress-induced reinstatement (Shaham et al. 2000a), DA activity in prefrontal cortical areas, including the PFC (Capriles et al. 2003; Sanchez et al. 2003) and OFC (Capriles et al. 2003), appears to critically mediate these behaviors, in that DA receptor antagonist administration into these regions blocks stress-induced drug seeking. It has also been shown that corticotrophin-releasing factor (CRF) and norepinephrine (NE), likely involving interactions between the BNST and CeA (Erb et al. 2001), are critically and selectively involved in stress-mediated reinstatement. Intracerebroventricular (ICV) administration of CRF alone induces reinstatement of heroin (Shaham et al. 1997) or cocaine seeking (Buffalari et al. 2012), whereas ICV or intra-BNST administration of CRF antagonists (Shaham et al. 1997; Erb et al. 1998; Erb and Stewart 1999; Le et al. 2000) attenuates footshock-induced reinstatement. Similar attenuations in drug seeking have been noted following pretreatment with compounds that attenuate NE activity (Erb et al. 2000; Shaham et al. 2000b; Highfield et al. 2001), including intra-BNST or CeA administration (Leri et al. 2002). Taken together, it appears that CRF and NE activity within the BNST and CeA, as well as interactions of these systems with the NAcc (uniquely involving the shell; McFarland et al. 2004) and PFC, may be critically involved in stress-induced drug craving and relapse when addicts are exposed to stressful stimuli.

In summary, it appears that three distinct, yet overlapping, neurocircuits mediate relapse-like behaviors following exposure to drug-associated cues, drug, or stressful events (Kalisva and McFarland 2003; Shaham et al. 2003). Thus, although there are a number of unique aspects involved in each type of reinstatement, these data collectively suggest that projections from the VTA (all forms of reinstatement), limbic regions including the BLA (cue reinstatement), CeA, BNST, and NAcc shell (stress reinstatement) converge on motor pathways involving the dmPFC and NAcc core that represent a “final common pathway” for all three types of instigating factors in relapse. It should be noted, however, that recent discoveries have implicated other brain structures and neurotransmitter systems in drug seeking behaviors. As mentioned previously, a considerable amount of research has implicated the dorsal (Fuchs et al. 2005, 2007; Meyers et al. 2006; Atkins et al. 2008; Ramirez et al. 2009; Xie et al. 2010; Wells et al. 2011) and ventral (Rogers and See 2007; Lasseter et al. 2010b) hippocampus in cue-induced relapse, including discrete and contextual forms of associative learning. Additionally, a newly defined region, called the mesopontine rostromedial tegmental nucleus (RMTg; also known as the tail of the VTA) (Jhou et al. 2009; Kaufling et al. 2009; Lavezzi and Zahm 2011) has been implicated as potentially having a profound role in reward-related behaviors. Receiving projections from a number of regions, including the medial PFC, ventral pallidum, BNST and lateral habenula (Kaufling et al. 2009), and consisting primarily of GABAergic neurons, the RMTg projects to the VTA and has been implicated as likely having a modulatory role on VTA-mediated drug reward and relapse (Jalabert et al. 2011; Lecca et al. 2011). Another region that has received interest for its potential role in addiction, particularly nicotine dependence, is the pedunculopontine tegmental nucleus (PPTg) (Maskos 2008; Market al. 2011). Providing cholinergic innervation to the VTA, it has been suggested that the posterior PPTg is involved in drug reinforcement (Alderson et al. 2006), with lesion and/or selective nicotinic receptor antagonism studies demonstrating an attenuation of nicotine (Lanca et al. 2000; Corrigall et al. 2001) and cocaine self-administration behaviors (Corrigall et al. 2002). Providing cholinergic innervation to the VTA, it has been suggested that the posterior PPTg is involved in drug reinforcement (Alderson et al. 2006), with lesion and/or selective nicotinic receptor antagonism studies demonstrating an attenuation of nicotine (Lanca et al. 2000; Corrigall et al. 2001) and cocaine self-administration behaviors (Corrigall et al. 2002). Finally, the neuropeptide orexin (also known as hypocretin), which is predominantly located in neurons in the lateral hypothalamus, has recently been found to play a significant role in mediating drug addiction and relapse (Harris et al. 2005), including cocaine- (Boutrel et al. 2005; Smith...
et al. 2009, 2010; Zhou et al. 2012), heroin-(Smith and Aston-Jones 2012), ethanol- (Lawrence et al. 2006; Richards et al. 2008; Shoblock et al. 2011), and nicotine-seeking behaviors (Plaza-Zabala et al. 2010). Another neuropeptide, oxytocin, has also received some interest recently for its potential as a therapeutic for drug addiction (Sarnyai 2011; McGregor and Bowen 2012).

CONCLUSIONS
Drug addiction is a chronic disease that encompasses a large number of social, economic, and medical issues that can persist even years after abstinence (Meyer 1996). As such, a considerable amount of research has been devoted to understanding the behavioral and neurobiological mechanisms that mediate the transition from casual drug use to the loss of control and persistence of drug-seeking behaviors that characterize drug addiction and dependence. Using various animal models of addiction, researchers have been able to determine aspects of the fundamental neurobiology involved in drug seeking across the entire addiction cycle, including the acute reinforcing effects of drugs, the neuroadaptations that occur during the transition to drug dependence, and finally the relatively permanent alterations in these systems that leave an individual susceptible to relapse. Although the role of neurotransmitters/neuromodulators and neural systems can vary across drugs of abuse and stages of the addiction cycle, evidence shows that the mesocorticolimbic pathway, including the VTA, NAcc, amygdala, and prefrontal cortices via DA and glutamate pathways, play a significant role in addiction. With a better understanding of the neurobiological factors that underlie drug addiction, continued clinical and preclinical research will greatly facilitate the development of novel therapeutic interventions that may result in better, more effective treatment strategies for drug-dependent individuals.

ACKNOWLEDGMENTS
The work of the authors was supported by National Institutes of Health Grants P50 DA015369, P50 DA016511, P20 DA022658, R01 DA010462, and R01 DA021690.

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Cite this article as Cold Spring Harb Perspect Med 2013;3:a011916


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Neural Systems in Addiction

Cold Spring Harbor Perspectives in Medicine

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Cold Spring Harbor Laboratory Press

Downloaded from http://perspectivesinmedicine.cshlp.org/ on November 8, 2016 - Published by Cold Spring Harbor Laboratory Press
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Matthew W. Feltenstein and Ronald E. See

*Cold Spring Harb Perspect Med* 2013; doi: 10.1101/cshperspect.a011916 originally published online April 11, 2013

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