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4.27 Learning and Memory in Addiction

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4.27.1 Introduction

Addiction affects millions of compulsive drug users around the world. It contributes to or causes severe health problems, such as cancer (tobacco), heart disease (tobacco and stimulants), liver disease (alcohol), HIV (needle sharing), and death (tobacco, opioids, and alcohol). It is associated with major social problems, including organized, property, violent crime, accidents, poverty, homelessness, and incarceration. Addiction is construed as a chronic disease characterized by cyclical periods of intense use (compulsive drug use and compulsive drug seeking), quitting, the emergence of an abstinence syndrome that includes a brief physical withdrawal and a persistent negative emotional state (e.g., dysphoria, anxiety, irritability), cravings, and relapse (Jaffe, 1980; Koob and Volkow, 2016, 2010).

While drug use involves the direct pharmacological action of the drug, drug seeking and relapse occur when the drug is no longer physiologically active; relapse rates are often around 50% in unmedicated individuals even after detoxification and protracted abstinence (McLellan et al., 2000). As such, addiction has been thought of as a neuroadaptive process (Everitt et al., 2008; Everitt and Robbins, 2016; Hyman and Malenka, 2001; Kelley, 2004; Volkow et al., 2003; White, 1996). The fields of neurobiology of addiction and the neurobiology of learning and memory have identified shared neurocircuitry, molecular substrates, and plasticity mechanisms. Many theories of addiction now include principles of classical and instrumental learning and multiple memory systems to explain the persistent behavioral phenomena observed in addiction (Everitt and Robbins, 2016; Koob and Volkow, 2016). The overall hypothesis that addiction persists as a memory or memory-like process long after drug exposure has become widely accepted (Everitt and Robbins, 2016; Hyman, 2005; Hyman and Malenka, 2001; McLellan et al., 2000; Nestler, 2001; Robinson and Berridge, 2008; White, 1996), even if the evidence for it is somewhat limited. The aim of this chapter is to describe the ways in which learning and memory have been implicated in drug addiction.

4.27.2 Associative Learning and Memory in Addiction

Associative learning and memory were implicated in addiction long before there were formal accounts of classical (Pavlov, 1927) and instrumental (Skinner, 1938) conditioning or a description of multiple memory systems (e.g., habit learning, declarative memory) (Squire, 1986). Nearly two centuries ago, the Scottish surgeon Robert Macnish described the difficulty of treating

individuals with alcohol addiction in terms of a learned association between drugs and stimuli (e.g., people, places) driving habitual drug taking (Macnish, 1834; Siegel, 1999):

> Man is very much the creature of habit. By drinking regularly at certain times he feels the longing for liquor at the stated return of those periods…He even feels it in certain companies, or in a particular tavern at which he is in the habit of taking his libations. We have all heard the story of the man who could never pass an inn on the roadside without entering it and taking a glass…it is a good rule for drunkards to break all such habits…Let him…forswear the society of boon companions…Let him, if he can manage it, remove from the place of his usual residence and go somewhere else.
> Macnish (1834, p.208).

Early theories of the pathology in addiction, however, emphasized the role of physical dependence and withdrawal (Himmelsbach, 1942). Although no formal theoretical analysis of the involvement of learning was performed, these changes were generally thought of as nonassociative and involving processes like habituation, which at the time were often not regarded as "learning" per se.

In 1965, Abraham Wikler laid out a theory of addiction in terms of associative learning theory. Wikler proposed a two-stage model in which (1) neutral stimuli acquired conditioned responses associated with positively reinforced drug use via Pavlovian classical conditioning; and (2) that chronic drug use was maintained via instrumental conditioning, particularly negative reinforcement (Shaffer, 1984; Wikler, 1977, 1973, 1965; Wikler and Pescor, 1967). The observations that most drug classes directly or indirectly engaged the "reward" pathway (Stewart et al., 1984; Volkow and Morales, 2015; Wise and Bozarth, 1987) and that psychostimulants produce addiction without producing much physical dependence led to an emphasis on positive reinforcement. Together, these reinforcement theories provided a framework upon which many contemporary cellular/molecular, behavioral neuroscience, and cognitive models of addiction are built. Recently, much work has been devoted to identifying the neurocircuitry and neurobiology underlying drug conditioning using both animal models and human neuroimaging (Bossert et al., 2013; Cruz et al., 2013; Jasinska et al., 2014; Volkow and Morales, 2015).

4.27.2.1 Classical and Instrumental Drug Conditioning

It is now well established that stimuli (e.g., contexts, people, objects, internal states) can be classically conditioned to both the "pleasurable/rewarding" effects of drugs of abuse (e.g., high, euphoria), as well as the withdrawal-induced aversive states associated with drug abstinence (e.g., dysphoria, irritability, anxiety, pain). In other words, conditioned stimuli can produce both drug-like and/or drug-opposite physiological and behavioral effects. These conditioned effects have been documented across drug classes including opioids, psychostimulants, alcohol, and nicotine in both humans and animal models (Childress et al., 1999, 1986; Droungas et al., 1995; Kaplan et al., 1985; Ludwig and Wikler, 1974; O'Brien et al., 1998; Sideroff and Jarvik, 1980).

The explanation as to why some conditioned stimuli produce drug-like effects, while others produce drug-opposite effects remains unknown and is beyond the scope of this chapter (see Ehrman et al., 1992; Eikelboom and Stewart, 1982; Siegel, 1999; Staiger and White, 1988 for discussions). Briefly, it has been attributed to factors such as the type of stimulus (e.g., discrete consummatory versus preparatory environmental context), temporal pairing of the conditioned stimulus and the drug, the motivational state of the animal, as well as the appropriate identification of the unconditioned response (Eikelboom and Stewart, 1982). Some conditioned stimuli even produce transient drug-like physiological effects followed by drug-opposite effects, as shown in individuals with opioid or alcohol addiction (Staiger and White, 1988).

Regardless of how conditioned stimuli come to be associated with drug-like and/or drug-opposite effects, both conditioned reward and conditioned aversive states have been hypothesized to contribute to subjective drug craving in humans (Childress et al., 1986; Drummond et al., 1990; Gawin and Kleber, 1986; Koob, 2013; O'Brien et al., 1998; Siegel, 1989; Stewart et al., 1984). Recently, it has been reported that individuals with addiction even exhibit progressive increases in their sensitivity (i.e., autonomic and behavioral responsiveness) to drug-paired cues the longer they abstain from a drug (Bedi et al., 2011), a phenomenon referred to as "incubation of craving" (Grimm et al., 2001).

In addition to classical conditioning, goal-directed instrumental conditioning, namely positive and negative reinforcement, has been implicated in addiction. It is widely accepted that addictive drugs are positive reinforcers; they produce acute "pleasurable" effects (e.g., euphoria/high in the case of psychostimulants and opioids, relaxation in the case of alcohol), which increase the likelihood that the drug will be used again. It is hypothesized that drug-paired stimuli can become conditioned reinforcers and thus, maintain drug seeking and taking either by positive incentive states (i.e., positive reinforcement) or by removing aversive states (i.e., negative reinforcement) (Everitt and Robbins, 2016; Koob et al., 2014; O'Brien et al., 1998; Stewart et al., 1984). Indeed, some evidence suggests that encounters with drug-paired cues are associated with relapse in humans (Heinz et al., 2009; Zhou et al., 2009).

4.27.2.1.1 Conditioned Reward and Positive Reinforcement

In the 1920s, Light and Torrance (1929) described the phenomenon of conditioned reward: "It is not uncommon for one addict to give another a hypodermic injection of sterile water and the recipient to derive a 'kick' and become quiet". In this example, it was hypothesized that injecting water alone was able to elicit a conditioned positive response, or "kick," after needle injections had been repeatedly associated with drug-induced euphoria (Levine, 1974; Meyer and Mirin, 1979; O'Brien, 1974). Thus, the

injection produced a conditioned "drug-like" effect. O'Brien and others examined this phenomenon in a "seminaturalistic" drug-taking environment; subjects were injected with an opioid antagonist and allowed to self-administer vehicle or opioids. Subjects found both opioid and vehicle injections "pleasurable" (Meyer and Mirin, 1979; O'Brien, 1974). Gawin and Kleber (1986) observed a similar response in a clinical setting with patients addicted to psychostimulants. Patients with cocaine addiction reported intense positive craving when interacting with people with whom they had used cocaine, visiting neighborhoods in which they had used drugs, or even when having blood drawn for standard medical procedures (Gawin and Kleber, 1986). In animal models, psychostimulants induce hyperactivity and this effect can be conditioned to drug cues and contexts (Stewart et al., 1984).

Neutral stimuli associated with the positive reinforcing or rewarding effects of addictive drugs are thought to acquire positive motivational valence and increase drug seeking and taking when presented alone (Shaham et al., 2003, 1994; Stewart et al., 1984). This has been modeled in animals using associative learning paradigms like conditioned place preference (CPP) (Tzschentke, 2007, 1998). Generally, in CPP, one context is paired with drug administration and another is paired with vehicle. For most drug classes, animals show a strong preference for the drug-paired context, indicating that the drug was rewarding (Tzschentke, 2007, 1998). CPP is thought to reflect positive reinforcing, instrumental drug seeking, and/or Pavlovian approach behavior in response to a drug-paired context (Tzschentke, 2007, 1998).

Positive reinforcement is often modeled in a self-administration paradigm, where an animal has to perform a behavior, such as press a lever or nose poke, to receive a drug. Cue or context-induced reinstatement of drug seeking is frequently used to study the motivational properties of drug-paired stimuli (Bossert et al., 2013; Crombag et al., 2008; Venniro et al., 2016). Here, animals are trained to self-administer a drug in a particular context and with cues paired with drug intake. Next, instrumental responding is extinguished in the absence of the drug and drug-associated cues or contexts. Instrumental responding can then be reinstated following exposure to the drug cues or contexts. Incubation of craving, or the increased cue-induced drug seeking associated with prolonged withdrawal, has been observed across drug classes and for rodents and nonhuman primates (Grimm et al., 2001; Venniro et al., 2016; Weerts et al., 2006).

4.27.2.1.2 Conditioned Withdrawal-Induced Aversive States and Negative Reinforcement

In the 1950s Abraham Wikler observed that when patients with opioid addiction were talking about their drug use in therapy, they would begin to exhibit physical signs of withdrawal (e.g., tearing eyes, running noses) even if they were detoxified and in protracted abstinence. He reported that if individuals addicted to opioids were repeatedly injected with an opioid antagonist that precipitates the effects of opioid withdrawal, eventually vehicle injections alone were able to elicit physiological and motivational (i.e., aversive emotional states) withdrawal symptoms (Wikler, 1953). Charles O'Brien et al. (1998) continued this work and conducted conditioning studies examining the effects of drug-related cues on behavior in human subjects addicted to opioids, cocaine, alcohol, or nicotine. In a seminal experiment, abstinent patients addicted to heroin and maintained on methadone were repeatedly injected with a very low dose of an opioid antagonist paired with a tone and peppermint odor (O'Brien et al., 1977). O'Brien et al. (1977) found that presentation of the tone and odor along with a vehicle injection came to elicit both subjective reports of aversive states and autonomic signs of withdrawal (e.g., increased respiration and heart rate).

Clinically, there have been numerous reports of conditioned withdrawal-induced aversive states in individuals with addiction (Bradley et al., 1989; Khantzian, 1985; O'Brien, 1975; O'Brien et al., 1986; Unnithan et al., 1992; Wikler, 1973). Though we described opioid examples here, conditioned aversive states have been found for most drug classes, including psychostimulants (Ettenberg et al., 1999; Koob, 2013; Koob et al., 2014; Markou and Koob, 1991; Wenzel et al., 2014). It is hypothesized that stimuli conditioned to withdrawal-induced aversive states can also acquire motivational significance and lead to increased drug taking and seeking when presented alone (Kenny et al., 2006; Kenny and Markou, 2005; Koob, 2013). An individual learns (1) that stimuli paired with withdrawal are aversive (Pavlovian conditioning) and (2) that seeking and taking the drug will alleviate aversive states (negative reinforcement) (Evans and Cahill, 2016).

Similar to conditioned reward, conditioned withdrawal-induced aversive states have been modeled in animals. Place conditioning, specifically conditioned place aversion (CPA), is one popular model (Koob et al., 2014; Tzschentke, 2007, 1998). In CPA, one context is paired with spontaneous or pharmacologically precipitated withdrawal and another is paired with vehicle. Animals with chronic or repeated drug administration show a strong aversion for the context paired with withdrawal, reflecting its negative motivational properties. In contrast to CPP, CPA in animal models is thought to reflect a negative reinforcing, instrumental drug seeking behavior (Tzschentke, 2007, 1998). This paradigm has largely been tested with alcohol and opioids (Cunningham et al., 2006; Gracy et al., 2001; Heinrichs et al., 1995; Stinus et al., 2005, 1990), but the phenomena extend to psychostimulants (Ettenberg et al., 1999; Wenzel et al., 2014).

Conditioned withdrawal-induced aversive states have also been modeled in animals with chronic/repeated drug exposures using electrical brain stimulation (i.e., ICSS), where drug cues conditioned to drug abstinence are able to elicit increased stimulation thresholds, similar to those observed in drug withdrawal (Kenny et al., 2006; Kenny and Markou, 2005; Koob, 2013; Koob and Le Moal, 1997). In a self-administration example, nonhuman primates taking morphine 24 h per day were repeatedly given injections of an opioid antagonist paired with a light cue (Goldberg, 1976). Eventually, presentation of the light cue alone led to an increase in morphine responding. A similar effect has been found in rats, with the added observation that presentation of the cue alone induces a reward deficit as measured by ICSS, suggesting that drug use may increase to overcome predicted reward deficits and to avoid the onset of withdrawal (Kenny et al., 2006; Kenny and Markou, 2005).

4.27.2.2 Learning Theory in Theories of Addiction

The processes by which conditioned cues and contexts acquire motivational properties and individuals become more sensitive to these stimuli over time are incompletely understood. From a learning theory perspective, the reinforcement or the "stamping in" of an association (Thorndike, 1898) could happen between an unconditioned stimulus and a conditioned stimulus (Pavlov, 1927), a stimulus and an outcome (Skinner, 1938), and/or a stimulus and a response (Rescorla, 1991; Thorndike, 1898). The encoding, consolidation, and retrieval of each of these associations (i.e., the memory trace) can be strengthened by experience (Hogarth et al., 2013; Rescorla, 1991; Wise, 2008). Conditioned stimuli, unconditioned stimuli, outcomes, and responses can become associated in complex hierarchical relationships (Hogarth et al., 2013).

Different theories of addiction emphasize different aspects of learning (e.g., Pavlovian–instrumental transfer, conditioned incentive learning), which will not be discussed in detail here (see, for examples, Di Chiara, 2002, 1999; Hogarth et al., 2013; Robinson and Berridge, 2008; Torregrossa and Taylor, 2016). As an example, one theory suggests that aversive states set the stage for enhanced acquisition of conditioned stimulus–unconditioned stimulus associations during abstinence. In other words, abstinence enhances reward (heightens incentive learning) rather than promotes avoidance of withdrawal-induced aversive states (negative reinforcement) (Di Chiara, 2002; Hutcheson et al., 2001; Smith and Aston-Jones, 2014). Conditioned aversive states could also affect hedonic set points and enhance the efficacy of positive reinforcement when a drug is used (stimulus–outcome association) (Koob, 2013; Koob and Le Moal, 1997; Kreek and Koob, 1998).

Despite emphasizing different psychological mechanisms, most contemporary theories of addiction include a critical role for conditioning factors and learned associations of positive incentive states or relief from aversive states. It remains an open question, however, whether associative learning is what drives compulsivity in addiction and/or the transition from controlled, recreational drug use to uncontrolled, compulsive drug seeking (O'Brien et al., 1998). Compulsivity can be defined as "perseverative, repetitive actions that are excessive and inappropriate" (Berlin and Hollander, 2014). In the laboratory, compulsive drug seeking and taking are modeled in paradigms such as escalation of drug self-administration after extended (Edwards and Koob, 2013) or chronic, intermittent (Kawa et al., 2016) access, increased responding in the face of punishment or cost (e.g., progressive ratio, shift in behavioral economic demand or elasticity curves) (Kearns et al., 2016; Markou et al., 1993; Pelloux et al., 2007), resistance to extinction (Markou et al., 1993), and habitual drug taking (resistance to deevaluation) (Everitt and Robbins, 2016). Combining these paradigms with manipulations of molecular substrates or neurocircuitry implicated in associative learning may reveal a shared role in compulsivity in addiction (discussed in section Approaches to Understanding the Relationship Between Learning and Memory and Addiction).

4.27.2.3 Conditioning and Treatments for Addiction

Clinical anecdotes and experimental evidence support the hypothesis put forth by Wikler that at least some aspects of the drug experience are able to be conditioned (Wikler, 1965, 1948). Conceptualizing addiction in terms of conditioning has provided avenues for possible treatments. Treatments for addiction targeting the primary pharmacological actions of drugs of abuse have been largely unsuccessful with the possible exception of naltrexone (Everitt, 2014; Koob and Mason, 2016; Torregrossa and Taylor, 2016). Thus, there has been great interest in identifying the mechanisms underlying addiction-related neuroadaptations because extinction or induced amnesia of addiction-related memories could become a useful treatment for relapse and/or compulsive drug seeking. Rawson et al. (1986) found that individuals addicted to cocaine were more likely to remain abstinent if they received outpatient, rather than inpatient treatment. Gawin and Kleber (1986) attempted to explain this observation in terms of conditioning. They proposed that those individuals in inpatient treatment were more likely to experience drug cue-elicited craving because conditioned stimuli are often absent from the inpatient setting (Gawin and Kleber, 1986).

Cue exposure therapy attempts to prevent relapse by reducing the behavioral and physiological effects of drug cues through repeated pairings of the cues in the absence of the drug (i.e., extinction). Extinction can reduce some of the conditioned physiological effects elicited by drug cues as well as reduce subjective reports of craving (Everitt, 2014). Clinically, this approach has been largely unsuccessful, possibly, for various reasons, including spontaneous recovery and context specificity during extinction therapy (Conklin and Tiffany, 2002; Myers and Carlezon, 2012) [but see findings for individuals with alcohol addiction (MacKillop and Lisman, 2008; Stasiewicz et al., 2007)].

Recent work aims to identify pharmacological agents that enhance extinction and/or reduce cue reactivity (Everitt, 2014; Jasinska et al., 2014; Koob and Mason, 2016; Torregrossa and Taylor, 2016). Another approach is targeting memory reconsolidation, in which a memory is reactivated by briefly presenting drug conditioned stimuli (Lewis, 1979; Nader, 2015) followed by prolonged extinction trials (i.e., "superextinction"). Reactivation of the cue engages molecular mechanisms involved in the initial consolidation of the memory and the memory trace becomes labile (Nader, 2015). Xue et al. (2012) applied this procedure to individuals addicted to heroin. First, abstinent subjects briefly viewed a video of drug taking (memory reactivation). Then, the subjects viewed the video for a longer period of time (engaging extinction processes). Subjects who underwent this procedure reported less subjective craving and demonstrated decreased physiological responses when exposed to the video during a subsequent test. Intriguingly, there was also a significant reduction in relapse that persisted up to 6 months later (Xue et al., 2012). In the same study, Xue et al. (2012) showed that this effect could be modeled in animals: the memory retrieval-extinction procedure reduced cue-induced reinstatement of drug seeking in cocaine or heroin-taking rats.

4.27.3 Approaches to Understanding the Relationship Between Learning and Memory and Addiction

In the following sections, we describe three ways in which the relationship between learning, memory, and addiction has been framed (Everitt and Robbins, 2016; Hyman, 2005; Kelley, 2004; Nestler, 2001; Robbins and Everitt, 1999; Volkow et al., 2003). It is important to note that these frameworks are not mutually exclusive and that theories of addiction attempt an integrated view.

1. Learning, memory, and addiction interact, but are distinct processes.
2. Learning, memory, and addiction share neurocircuitry and molecular substrates.
3. Addiction as an example of pathological learning.

4.27.3.1 Learning, Memory, and Addiction Interact, but Are Distinct Processes

In this framework, addiction is thought to include aspects of associative learning and memory, but ultimately, other mechanisms are thought to cause the behavior in addiction to be pathological. More specifically, while drug cue-elicited craving may share neuroadaptations similar to those underlying traditional associative learning, the process of addiction includes behaviors and neuroadaptations that are dissociable from associative learning and memory (e.g., sensitization, allostasis, loss of inhibitory control) (Anagnostaras et al., 2002; Anagnostaras and Robinson, 1996; Koob, 2013; Koob and Le Moal, 1997; Robinson and Berridge, 1993, 2008; Volkow et al., 2003; Volkow and Morales, 2015). From a treatment perspective, this view implies that behavioral or pharmacological manipulations that selectively target associative learning and memory mechanisms will have limited efficacy in treating addiction (but see Xue et al., 2012).

In the following quote, Nora Volkow, current director of the U.S. National Institute of Drug Abuse, describes a putative role for learning and memory in addiction:

> Memory systems are likely to be involved in the process of addiction via their influence on drug intoxication and craving. In drug intoxication, the previously learned drug experience will set the expectations of the drug effects in the drug abuser, which in turn will affect his or her response to the drug…Drug craving is associated with the learned response that links the drug and its environment to a pleasurable or an intensely overpowering experience. The relevance these learned associations have on addiction is evidenced by the pernicious effect that a place, a person, or a cue—that brings back memories of the drug—have on the addict who is trying to stay clean.
>
> Volkow et al. (2002, p. 618).

In support of this role, early neuroimaging work using functional magnetic resonance imaging and positron emission tomography in humans demonstrated that the amygdala and hippocampus, brain regions strongly linked to associative learning and contextual and declarative memory, respectively, were strongly activated during drug intoxication (Stein et al., 1998) and craving (Childress et al., 1999; Grant et al., 1996; Jasinska et al., 2014; Kilts et al., 2001).

Recent work combining drug cue reactivity paradigms with human neuroimaging has examined the neurocircuitry underlying cue-elicited craving (Jasinska et al., 2014; Koob and Mason, 2016). In these tasks, subjects are exposed to drug cues (e.g., auditory, visual, tactile, gustatory, or multisensory) while subjective and physiological reactivities are measured (Childress et al., 1999; Jasinska et al., 2014; Volkow et al., 2009, 2003). Cue reactivity has been shown to correlate with addiction severity and treatment effectiveness (Jasinska et al., 2014). In addition to the hippocampus and amygdala, salient drug cues evoke activity in the ventral tegmental area (VTA), ventral striatum, anterior cingulate cortex, prefrontal cortex (PFC, including the orbitofrontal cortex and dorsolateral PFC), and insula, as well as the dorsal striatum and sensory and motor cortices (Jasinska et al., 2014; Volkow et al., 2011; Yalachkov et al., 2012).

From a neurocircuitry perspective, while learning and memory circuits may be involved, several other circuits are theorized to be key to compulsivity and transition to addiction. For example, reward (ventral striatum and pallidum), motivation/drive (orbitofrontal cortex), executive/inhibitory control (PFC and anterior cingulate gyrus), and stress circuits (extended amygdala, ventral striatum, habenula) may all be dysfunctional (Koob and Volkow, 2016; Volkow et al., 2009, 2003). There is even some evidence of dysfunctional perceptual and sensory processing circuits (Jasinska et al., 2014). One example of the importance of dysregulation in circuits other than those implicated in learning and memory is the observation that abstinent individuals with cocaine addiction have reduced dopamine release in the dorsal striatum, as well as reduced D2 receptor expression (Volkow et al., 1997). This observation led to the notion that frontal-mediated executive control circuits have impaired ability to inhibit habitual responding. Recently, treatment efficacy in individuals with alcohol addiction has been linked to the degree of frontal cortex executive dysfunction (Rando et al., 2011).

From a molecular perspective, addiction is hypothesized to recruit multiple forms of plasticity, which may only partially overlap with the neural plasticity underlying traditional associative learning and memory (i.e., dopamine and glutamate signaling) (Anagnostaras et al., 2002; Anagnostaras and Robinson, 1996; Koob and Volkow, 2016; Volkow et al., 2011; Volkow and Morales, 2015). For example, behavioral sensitization, the progressive increase in a behavioral response following repeated administration of a drug, can develop in the absence of glutamate neurotransmission through *N*-methyl-D-aspartate (NMDA) receptors, a hallmark of cellular models of associative learning and memory (Carmack et al., 2013). In the following two sections, we will describe two theories of addiction in which nonassociative mechanisms are the ones hypothesized to be driving pathological behavior in addiction.

4.27.3.1.1 Positive Reinforcement Theories: Incentive Sensitization

The mesocorticolimbic dopamine pathway, particularly the projection from the VTA to the nucleus accumbens (ventral striatum in humans), plays a key role in incentive salience, directing behavior toward salient stimuli (Schultz, 2007). It was frequently referred to as the "reward" pathway (Wise, 2008), but incentive salience reflects a more accurate description of the functional attributes of this system. Incentive salience is the motivation for a reward driven both by previously learned associations between conditioned and unconditioned stimuli and an organism's physiological state (Koob and Volkow, 2016). In a seminal study, Schultz et al. (1997) demonstrated that VTA dopamine cells in nonhuman primates initially fired action potentials in response to the delivery of a predictable nondrug, food reward. Eventually, the cells fired only when the subject was exposed to conditioned stimuli that predicted the reward, but not to the reward itself (Schultz et al., 1997). Thus, it was hypothesized that the cue acquired incentive salience.

The mesocorticolimbic dopamine pathway appears to be critically involved in the acute reinforcing actions of many classes of drugs despite the different classes having diverse primary pharmacological actions. Direct or indirect drug-induced dopamine release in the nucleus accumbens has been demonstrated for psychostimulants, opioids, nicotine, cannabinoids, and alcohol (Volkow and Morales, 2015). In addition to dopamine, opioid peptides are required for the rewarding effects of opioids and alcohol and contribute to the rewarding effects of psychostimulants and cannabinoids (Le Merrer et al., 2009; Volkow et al., 2011). The VTA also has major dopaminergic projections to the dorsal striatum, amygdala, PFC, and anterior cingulate cortex (Koob and Volkow, 2010; Swanson, 2000). There is a projection from the VTA to the hippocampus (Swanson, 2000), but there is some debate as to whether or not this projection is dopaminergic (Broussard et al., 2012). Salient drug-paired stimuli induce dopamine release in the dorsal and ventral striatum, amygdala, and PFC and opioid peptides in the anterior cingulate and frontal cortex (Ito et al., 2002; Koob and Volkow, 2016; Stewart et al., 1984). Recent work using fast-scan cyclic voltammetry in rats has found decreased dopamine release in the nucleus accumbens in response to cocaine following extended drug access in the escalation of self-administration model (Willuhn et al., 2014), but a dramatic increase in dopamine release to drug-paired cues (Burgeno et al., 2015). This work extends the seminal findings of Schultz et al. (1997) with food rewards to drug self-administration.

According to the incentive sensitization theory of addiction, repeated, intermittent drug use causes the stored incentive value of the drug to undergo nonassociative sensitization in which the unconditioned response to the drug progressively increases [i.e., stimulates more dopamine release in the nucleus accumbens/ventral striatum, but see Willuhn et al., (2014)]. This leads to excessive motivation or attributed salience to the drug, drug cues, or emotional states (Robinson and Berridge, 1993, 2008). This is reflected by increased dopamine release in response to drug-paired cues versus neutral cues, which motivates drug taking even when the drug's pharmacological effects have decreased as a result of chronic use (Koob and Mason, 2016; Schultz et al., 1997; Volkow et al., 2014). As a result, individuals with addiction are driven to approach and pursue incentive cues, contexts, and emotional states.

Associative learning is thought to contribute to the sensitized drug response through excitatory Pavlovian conditioning producing an additional conditioned response and/or inhibitory occasion-setting gating the expression of sensitization in the presence of contexts or cues where the drug is not expected (Anagnostaras et al., 2002; Anagnostaras and Robinson, 1996). An alternative associative learning account to the incentive-sensitive sensitization theory posits that addiction develops as a result of abnormal Pavlovian incentive learning, mediated by nonadaptive dopamine release in the nucleus accumbens shell (Di Chiara, 2002). In this conception, the acquisition of the incentive conditioned stimulus–unconditioned stimulus association is pathological, rather than the expression of the behavioral response.

4.27.3.1.2 Negative Reinforcement Theories: Opponent Process and Allostasis

In one negative reinforcement theory of addiction, homeostatic mechanisms such as allostasis (defined as maintenance of physiological stability with change, often a set point change) drive drug taking (Edwards and Koob, 2010; Koob and Le Moal, 1997; Siegel, 1999; Solomon and Corbit, 1974; Wikler, 1965). According to opponent process theories, it is theorized that nonassociative, counteradaptive mechanisms cause allostasis or a long-lasting change in an organism's hedonic set point (Koob and Le Moal, 2001). Allostasis, in this context, could be termed hedonic allostasis and is reflected by the emergence of an aversive state in individuals with addiction who are in withdrawal or protracted abstinence. Aversive states are thought to be caused by (1) reduced reward system function, which can be measured using electrical brain stimulation in animal models as well as responses to natural rewards (dysregulated mesocorticolimbic dopamine system) (Koob, 2013; Koob et al., 2014; Koob and Le Moal, 1997; Volkow et al., 2003); and (2) the engagement of brain and hormonal stress systems (e.g., corticotropin-releasing factor, dynorphin, and norepinephrine recruitment in the extended amygdala and habenula) (Koob et al., 2014). Aversive states occur across drug classes and can be paired to stimuli (Kenny et al., 2006; Kenny and Markou, 2005; Koob, 2013; Markou and Koob, 1991). Though hedonic allostasis is thought to be a nonassociative key factor driving compulsivity and the transition to addiction, there is a role for associative learning in the form of (1) conditioned cues and contexts, which could acquire incentive salience, and (2) aversive events activating a learned association of drug use to alleviate aversive states (Evans and Cahill, 2016). For example, rats self-administering heroin were trained to associate a light and tone cue with injections of an opioid antagonist. Eventually, rats increased heroin intake during presentation of the light and tone cue, but in the absence of the antagonist, presumably to avoid the onset of withdrawal (Kenny et al., 2006). It is unknown whether such conditioned stimuli sensitize, incubate, or otherwise follow the rules of stimuli paired with drug reward.

4.27.3.2 Learning, Memory, and Addiction Share Molecular Substrates and Neural Circuits

In this framework, neuroadaptations as a result of drug exposure are thought to reflect the same neurobiological processes as memory, particularly at the molecular level, because the brain likely has a limited number of plasticity mechanisms to remodel synapses (Nestler, 2001). According to cellular and molecular theories of addiction, addiction is then seen as a type of drug-induced neural plasticity (Hyman, 2005; Nestler, 2004; Russo et al., 2010). Similarly, memory and addiction are increasingly thought to share a neural substrate, whereby learning caused by drug exposure produces neuroadaptations in the motivational circuitry related to natural reward learning (Kelley, 2004), as well as other memory systems (Kutlu and Gould, 2016; White, 1996).

4.27.3.2.1 Molecular Substrates

Learning can be defined as a relatively permanent change in behavior as the result of experience. Experiences are hypothesized to modify synaptic plasticity in a way that is reflected in future behavior. Though it is unknown exactly how synaptic plasticity leads to the encoding, storage, and retrieval of experiences (i.e., memory traces), synaptic plasticity appears to be required for all types of memories (e.g., hippocampus for declarative memory, basal ganglia for habit learning) (Citri and Malenka, 2008; Kandel et al., 2014; Mayford et al., 2012; Sweatt, 2016). The plasticity molecules recruited in various forms of learning and memory overlap and are conserved across species, including aplysia, *drosophila*, mice, rats, and humans (Citri and Malenka, 2008; Kandel et al., 2014; Mayford et al., 2012; Sweatt, 2016).

Cellular and molecular models of associative learning and memory have several well-established phenomena, including, but not limited to, (1) associative stimulation activating glutamatergic α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and NMDA receptors at select synapses (Citri and Malenka, 2008); (2) calcium entry into the cell through NMDA receptors; (3) activation of persistent protein kinases by signaling cascades [e.g., protein kinase A (PKA), protein kinase C (PKC), calcium/calmodulin-dependent protein kinase II (CaMKII)] (Silva et al., 1992a, 1992b); (4) new gene transcription activated by calcium-responsive transcription factors [e.g., cAMP response element–binding protein (CREB)] and protein synthesis (Josselyn et al., 2001; Kida et al., 2002); (5) parallel processes in long-term potentiation and depression (LTP and LTD) (Bliss and Collingridge, 1993; Bliss and Lomo, 1973); and (6) structural remodeling of the neuronal synapse in an input-specific manner (Bailey et al., 2015; Bosch et al., 2014). Interfering with these neuroplastic changes results in amnesia.

The specificity of drug cue conditioning and conditioned cue behaviors to individuals (Gawin and Kleber, 1986) led to the hypothesis that one mechanism underlying addiction was synapse-specific associative learning (Hyman and Malenka, 2001). Therefore, as summarized in the following quote, a major focus in drug addiction research has been to identify plasticity molecules:

> Drugs of abuse cause long-lasting neural changes in the brain that underpin the behavioral abnormalities associated with drug addiction…the molecular pathways of learning and memory on the one hand, and of drug addiction on the other, have converged. Learning and memory and drug addiction are modulated by the same neurotrophic factors, share certain intracellular signaling cascades, and depend on activation of the transcription factor CREB. They are associated with similar adaptations in neuronal morphology, such as the formation or loss of dendritic spines. Even more compelling, they are accompanied by alterations in neural plasticity at glutamatergic synapses.
>
> Nestler (2001).

There are many examples of shared molecular substrates between learning and memory and addiction, corresponding to steps (1)–(5) (Carlezon et al., 1998; García-Pardo et al., 2016; Howell et al., 2014; Lüscher and Malenka, 2011; Nestler, 2004; Russo et al., 2010; Thomas et al., 2009; Wolf and Ferrario, 2010). Only a few will be described here.

As described in section Positive Reinforcement Theories: Incentive Sensitization, the mesocorticolimbic dopamine pathway is critical for the acute reinforcing effects of most drug classes. It is also involved in assigning incentive salience to drug-paired stimuli. Therefore, the cellular/molecular biology of addiction field has heavily focused on synaptic plasticity in this pathway. It has been hypothesized that medium spiny neurons within the nucleus accumbens are "coincidence detectors" in associative learning in addiction, in a manner similar to that of pyramidal cells within the cortex for learning and memory (Kelley, 2004). One hallmark of LTP in the pyramidal hippocampal–PFC pathway is the coactivation of dopamine (D1) and glutamate receptors (Baldwin et al., 2002). Here, glutamate is theorized to encode the specific sensorimotor experience, while dopamine is thought to detect rewarding, salient events, or unpredictable events (Abel and Lattal, 2001; Kelley, 2004). A single exposure to psychostimulants has been shown to induce LTP (potentiate AMPA currents) in VTA dopamine cells and this effect requires dopamine D1 receptors (Ungless et al., 2001). Indeed, most drug classes evoke LTP- and LTD-like plasticity in VTA dopamine neurons (Lüscher and Malenka, 2011; Volkow and Morales, 2015).

Drug-induced LTP- and LTD-like plasticity requires glutamatergic signaling through NMDA receptors (Russo et al., 2010; Thomas et al., 2009). Glutamatergic inputs to the nucleus accumbens have been found from the amygdala, hippocampus, and PFC (Volkow and Morales, 2015). Much evidence demonstrates altered glutamatergic and dopaminergic signaling following chronic drug abuse, particularly in the nucleus accumbens, PFC, and VTA (Hotsenpiller and Wolf, 2003; Kenny et al., 2003a,b; Koob et al., 1998; Koob and Volkow, 2016; Lovinger et al., 2003; Pierce et al., 1996; Pierce and Kalivas, 1997). A smaller literature has also indicated alterations in the hippocampus and amygdala (Everitt et al., 2008, 2001).

At the behavioral level, blocking glutamate and dopamine signaling interferes with conditioned drug effects, including CPP, cue and context-induced reinstatement, and incubation of craving (Bossert et al., 2011; Conrad et al., 2008; Schmidt et al., 2015;

Tzschentke, 2007; Wolf, 1998). Administration of *N*-acetylcysteine, a drug that normalizes glutamatergic transmission in the nucleus accumbens, to animals trained to self-administer cocaine enhances extinction learning and blocks cue-induced reinstatement (Baker et al., 2003; LaRowe et al., 2013; Moran, 2005; Moussawi et al., 2011). In double-blind placebo-controlled clinical trials, however, *N*-acetylcysteine has weak effects in humans (Gray et al., 2012; Heilig et al., 2016; LaRowe et al., 2013). D-cycloserine, a partial agonist at the glycine site of the NMDA receptor, enhances extinction of drug memories and has some efficacy in reducing cue reactivity in smokers, but is ineffective in individuals addicted to cocaine or alcohol (Myers and Carlezon, 2012).

In another example, the PKA pathway plays a major role in learning and memory (García-Pardo et al., 2016). Chronic exposure to addictive drugs increases cAMP formation in the nucleus accumbens, which subsequently activates PKA and CREB (Carlezon et al., 1998; Nestler, 2004). Interfering with this signaling pathway has profound effects on addiction-like behavior. Tonic activation of the cAMP/PKA pathway promotes escalation of drug self-administration (Edwards and Koob, 2010; Self et al., 1998); blockade of the pathway blocks reconsolidation of cued-cocaine memories (Sanchez et al., 2010).

As a final example, chronic psychostimulant administration produces structural remodeling (increased spine density) in medium spiny neurons of the nucleus accumbens (Robinson and Kolb, 1997; Russo et al., 2010). Increased spine formation may occur following insertion of high-calcium-permeable AMPA receptors (Conrad et al., 2008). The protein kinase mTORC1 is implicated in learning and memory as it mediates dendritic translation of synaptic proteins. Addictive drugs activate the mTORC1 pathway in the nucleus accumbens, as well as the hippocampus, PFC, and amygdala (Neasta et al., 2014). Blockade of this pathway interferes with memory reconsolidation and blocks cued reinstatement of alcohol seeking (Barak et al., 2013; Ron and Barak, 2016).

4.27.3.2.2 Neurocircuitry

Traditionally, the fields of learning and memory and of addiction have examined separate brain regions and brain circuits. The addiction field targeted the connections and terminals of the mesocorticolimbic dopamine system, while the memory field focused primarily on the hippocampus (declarative and contextual learning) and amygdala (associative conditioning) (Kandel et al., 2014; Tonegawa et al., 2015; Volkow et al., 2003). Increasingly, the anatomical distinction between these two fields has blurred (Everitt and Robbins, 2016; Goodman and Packard, 2016; Kelley, 2004; Kutlu and Gould, 2016; Rosen et al., 2015; White, 1996).

Experimental evidence strongly supports the existence of multiple memory systems mediated by distinct brain regions (e.g., hippocampus, amygdala, dorsal striatum) and neural circuits for encoding, consolidation, and retrieval (McDonald and White, 1993; Squire, 1986). Two decades ago, Norman White extended the multiple memory systems model to drug addiction (White, 1996), implicating the hippocampus in contextual control of drug seeking, the amygdala in conditioned associations between stimuli and drug use, and the dorsal striatum in habitual drug seeking (Goodman and Packard, 2016). Converging findings from human and animal studies support this view, demonstrating that behavioral phenomena associated with drug use (e.g., CPP, CPA, conditioned responding, reinstatement of self-administration) engage the hippocampus, amygdala, and dorsal striatal-dependent memory systems (Everitt and Robbins, 2016; Goodman and Packard, 2016; Kelley, 2004; Kutlu and Gould, 2016; Rosen et al., 2015; White, 1996). For example, the basolateral amygdala is critical for cue-induced reinstatement of drug seeking for psychostimulants, alcohol, and opioids (Bossert et al., 2013), as well as conditioned withdrawal produced by a conditioned stimulus previously paired with an opioid antagonist in morphine-dependent rats (Schulteis et al., 2000); and specific patterns of neuronal activity in the hippocampus are required for expression of cocaine-induced CPP (Trouche et al., 2016).

It is important to note that the multiple memory systems are not entirely independent of one another and indeed can interact or even compete (Poldrack and Packard, 2003). This has been demonstrated for certain motor sequence learning and maze learning tasks (Baudonnat et al., 2011; Goodman and Packard, 2016; Kathirvelu and Colombo, 2013; McDonald and White, 1993; Schroeder et al., 2002). For example, hippocampus lesions in rats enhance acquisition of the dorsal striatal-dependent win–stay version of the radial arm maze task (McDonald and White, 1993). Therefore, Goodman and Packard (2016) have advised caution in assigning roles to memory systems in addiction. For instance, they suggest that drugs with addictive potential could modulate habit learning by directly activating the dorsal striatum; alternatively, they could impair hippocampus function and therefore, indirectly enhance dorsal striatal function (Goodman and Packard, 2016). This is an open area for investigation.

Recently, it has been theorized that drugs with addictive potential act, themselves, to directly enhance memory consolidation at a cellular and/or systems level in multiple memory systems. This could then lead to increased drug seeking and taking (Goodman and Packard, 2016; Rosen et al., 2015). At present, few studies have directly explored the neurocircuitry underlying consolidation of drug memories (Gholizadeh et al., 2013; Hsu et al., 2002; Rosen et al., 2015; Tzschentke, 2007). Some evidence has implicated the hippocampal–cortical (Anagnostaras et al., 2001; Maren, 2001) and basolateral amygdala–PFC circuits identified in the consolidation of emotional (fear) memories (Frankland, 2004; Nader, 2015) in consolidation of drug-induced CPP (Rosen et al., 2015; Sun et al., 2011; Tzschentke, 2007). Gholizadeh et al. (2013) used protein synthesis inhibition to show that early consolidation (0–6 h) of morphine-induced CPP requires the basolateral amygdala, while late consolidation (6–12 h) requires the PFC (Gholizadeh et al., 2013). The majority of research has instead focused on identifying the neurocircuitry-mediating acquisition and expression of drug memories. In the following sections, we describe a few examples of overlap between the neuroanatomy underlying multiple memory systems and drug addiction.

4.27.3.2.2.1 Hippocampus-Dependent Learning

The hippocampus has a well-established role in the formation of declarative memories—or the explicit knowledge of the relationship between stimuli (Kutlu and Gould, 2016). One prominent feature of the hippocampus is its high degree of synaptic plasticity (Citri and Malenka, 2008; Kandel et al., 2014), which is thought to enable the encoding of complex contextual and spatial

information. The hippocampus is implicated in behaviors related to drug addiction (Goodman and Packard, 2016; Kutlu and Gould, 2016). For example, the dorsal hippocampus is involved in context-induced reinstatement and CPP, particularly for psychostimulants (Bossert et al., 2013; Trouche et al., 2016; Tzschentke, 2007). In recent work, Trouche et al. (2016) used a transgenic mouse model to selectively label neurons activated in the hippocampus during acquisition of cocaine-induced CPP. Subsequent optogenetic silencing of these previously active neurons completely blocked the expression of cocaine CPP. At the cellular level, acute or chronic administration of drugs with addictive potential modifies hippocampal-dependent LTP (Kutlu and Gould, 2016; Lüscher and Malenka, 2011). Additionally, opioids, psychostimulants, and alcohol interfere with neurogenesis in the adult hippocampus (Eisch and Harburg, 2006; Golub et al., 2015), which may affect normal functioning.

Noteworthy, though certain drug-associated memories require the hippocampus, chronic drug exposure affects hippocampus-dependent memory in both humans and animals. Individuals with opioid, psychostimulant, or alcohol addiction exhibit impaired hippocampus-dependent memory, including episodic memories, even in protracted abstinence (Curran et al., 2001; Kutlu and Gould, 2016; Wood et al., 2014). Animals given high doses of psychostimulants, alcohol, or opioids exhibit significantly impaired hippocampus-dependent learning on tasks such as contextual fear conditioning, spatial object recognition, Morris water maze, and the T-maze (Belcher et al., 2008; Gulick and Gould, 2007; Kutlu and Gould, 2016; Mendez et al., 2008; North et al., 2013; Tramullas et al., 2008; Wood et al., 2014; Zhou et al., 2015). In an attempt to reconcile these observations, Kutlu and Gould (2016) hypothesized that initial exposure to low doses of psychostimulants and alcohol may actually enhance hippocampal function (Wood et al., 2014) and promote the formation of drug–context associations, while later chronic or high dose drug use impairs hippocampal function, resulting in reduced cognitive flexibility, which prevents the reversal of maladaptive context associations through new learning.

4.27.3.2.2.2 Mesocorticolimbic and Corticostriatal Reward Learning

It has been postulated that addictive drugs act on the same neurocircuits that are critical for normal reinforcement learning and that this property is fundamental to their ability to establish behaviors associated with addiction (described in section Positive Reinforcement Theories: Incentive Sensitization) (Kelley, 2004). The dopamine–glutamate interactions within the mesocorticolimbic and corticostriatal networks described earlier are thought to play a critical, integrative role in appetitive instrumental learning. In support of this hypothesis, drug-induced dopamine release in the nucleus accumbens shell is three to five times higher than the amount of dopamine released in response to natural reinforcers (Di Chiara, 2002; Wise, 2008). Further, dopamine release induced by natural reinforcers generally undergoes one-trial habituation in the nucleus accumbens shell, but dopamine release in response to drug administration or drug cue presentation does not habituate (Di Chiara et al., 1999). As such, drug addiction has been referred to as a dopamine-dependent associative learning disorder, whereby appetitive instrumental learning is directed toward drugs and conditioned stimuli (Di Chiara, 2002, 1999; Di Chiara et al., 1999) to the detriment of natural reinforcers (Koob, 2013; Volkow et al., 2003). In the strongest version of this argument, the mesolimbic and mesocortical dopamine systems implicated in addiction are thought to be the same those involved in habit learning (discussed in more detail in the following section) (Everitt and Robbins, 2016; Kelley, 2004).

4.27.3.3 Drug Addiction as an Example of Pathological Learning

Finally, addiction has been described as primarily a "disease of learning and memory" (Hyman, 2005). In this conception, addictive drugs are thought to hijack the adaptive mechanisms underlying the natural reinforcement (incentive) pathway and recruit maladaptive habit learning directed at drug seeking and taking (Berke and Hyman, 2000; Everitt and Robbins, 2016; Hyman, 2005; Hyman and Malenka, 2001; Tiffany, 1990; Torregrossa and Taylor, 2016; White, 1996). The following quote captures this view:

> …addiction represents a pathological usurpation of the neural mechanisms of learning and memory that under normal circumstances serve to shape survival behaviors related to the pursuit of rewards and cues that can predict them.
>
> Hyman (2005).

Goal-directed instrumental learning is one of the phylogenetically oldest forms of behavioral adaptation; it enables organisms to seek mates, avoid danger, fight predators, and seek stimuli necessary for survival, such as food and water (Dickinson and Balleine, 1994; Kelley, 2004). The diverse molecular substrates underlying instrumental learning are thought to ensure specificity and plasticity in this adaptive system. Interoceptive (e.g., thirst, hunger, internal timing) and external cues (e.g., smell of food) drive behavior toward obtaining goals. The mesocorticolimbic dopamine system described in section Positive Reinforcement Theories: Incentive Sensitization is theorized to be the neural reinforcement/reward/incentive pathway. According to the drug addiction as pathological learning framework, addictive drugs first "take over" the goal-directed incentive pathway (Hyman, 2005). Interoceptive cues (e.g., craving or emotional states) and external cues (e.g., drug environments, drug paraphernalia, people) conditioned to drug effects also now drive drug seeking and consumption (Everitt and Robbins, 2016).

As an individual progresses to addiction, it is theorized that there is a transition from goal-directed instrumental behavior to automatic, habitual behavior (Tiffany, 1990) through engagement of spiraling basal ganglia–globus pallidus–thalamic cortical

loops (Belin et al., 2009; Belin and Everitt, 2008; Everitt, 2014; Everitt and Robbins, 2016; Hyman, 2005; Hyman and Malenka, 2001). The nigrostriatal system is linked to habit/procedural learning and voluntary motor control and comprises mainly dopamine projections from the substantia nigra to the caudate and putamen (dorsal striatum in humans) and globus pallidus. In this model, repeated activation of the nucleus accumbens incentive system by drugs or conditioned stimuli engages the habit formation system, particularly the dorsal striatum (Belin et al., 2009). Whereas goal-directed drug seeking is elicited by the anticipated incentive value of the drug or drug-paired stimulus, habitual drug seeking is elicited by stimuli that have formed a direct association with the drug seeking response (Everitt and Robbins, 2016; Hogarth et al., 2013; Robbins and Everitt, 1999; Torregrossa and Taylor, 2016). In other words, presentation of the drug or drug cue automatically triggers behaviors aimed at obtaining the drug. This is hypothesized to occur for both the pursuit of positive incentive states and perhaps also for the habitual avoidance of withdrawal-induced aversive states (Koob and Volkow, 2016).

Evidence for a transition from the ventral to dorsal striatum comes from both human neuroimaging and animal models (Belin and Everitt, 2008; Corbit et al., 2014, 2012; but see Willuhn et al., 2014; see the following for reviews Belin et al., 2009; Everitt, 2014; Everitt and Robbins, 2016; Torregrossa and Taylor, 2016). Neuroadaptations in the nucleus accumbens appear early into drug use, while neuroadaptations in the dorsal striatum do not appear until much later (Letchworth et al., 2001). Additionally, cue-induced reinstatement of cocaine self-administration involves dopamine and AMPA receptor modulation in the dorsal striatum in rats with a long history of cocaine administration (Vanderschuren et al., 2005). In contrast, dopamine signaling in the nucleus accumbens, but not the dorsal striatum (caudate nucleus), is required for the acquisition of conditioned amphetamine responding (Taylor and Robbins, 1986). Recently, Willuhn et al. (2012) provided compelling evidence for this transition using in vivo cyclic voltammetry to show that drug cue-evoked dopamine release in the dorsolateral striatum emerged over several weeks in rats self-administering cocaine, while dopamine release in the nucleus accumbens core decreased over the same time period. Phasic dorsal striatal dopamine release was completely blocked by nucleus accumbens core lesions, suggesting a hierarchical relationship between the two regions (Willuhn et al., 2012). However, the transition in the neurocircuit was not related to compulsive or escalated cocaine use in the animal model (Willuhn et al., 2012). Finally, drug cue-elicited activation of the dorsal striatum has been observed in individuals with addiction across different drug classes; the magnitude of dorsal, but not ventral, striatal activation correlated with addiction severity and how automatic a behavior was in response to presentation of a drug cue (Jasinska et al., 2014; Yalachkov et al., 2012).

In addition to the recruitment of maladaptive habit learning following the usurpation of the incentive pathway, the process of addiction is also theorized to involve pathological learning associated with negative reinforcement as part of the "dark side of addiction"—or the reduced function of reward neurocircuitry and the recruitment of antireward systems (see section Negative Reinforcement Theories: Opponent Process and Allostasis) (Koob et al., 2014; Koob and Le Moal, 2005). As described in section Conditioned Withdrawal-Induced Aversive States and Negative Reinforcement, aversive-like responses are a common response to acute withdrawal and protracted abstinence for all major classes of drugs with addictive potential. Individuals with addiction learn both (1) that stimuli paired with drug withdrawal are aversive via classical conditioning (conditioned withdrawal) and (2) that seeking and taking the drug will alleviate these aversive states (Evans and Cahill, 2016; Kenny et al., 2006; Koob et al., 2014). The neural circuit that subserves this type of associative learning is hypothesized to overlap with the neural circuit underlying aversive fear learning, which includes the basolateral amygdala, central nucleus of the amygdala, bed nucleus of the stria terminalis, and periaqueductal gray (Avery et al., 2016; Janak and Tye, 2015; Maren, 2001; McNally et al., 2011; Sweatt, 2016), and possibly the hippocampus (specifically recruited in contextual fear conditioning) (Anagnostaras et al., 2001; Gale et al., 2004). As with unconditioned fear, this circuit is activated during unconditioned, acute drug withdrawal as measured by immediate-early gene expression (Frenois et al., 2002; Gracy et al., 2001). Structures in this circuit have been implicated in the acquisition and expression of conditioned withdrawal-induced aversive states (Evans and Cahill, 2016; Heinrichs et al., 1995; Schulteis et al., 2000; Stinus et al., 1990; Wenzel et al., 2014). For example, basolateral amygdala lesions reduced the acquisition of conditioned withdrawal to a light and tone cue paired with naloxone in opioid-dependent rats (Schulteis et al., 2000). A corticotrophin-releasing factor (CRF) peptide antagonist injected into the central nucleus of the amygdala blocked the expression of CPA produced by an opiate-antagonist injection in morphine-dependent rats (Heinrichs et al., 1995). Additionally, norepinephrine antagonism in the central amygdala or bed nucleus of the stria terminalis prevented the acquisition of CPA for the delayed effects of cocaine (i.e., negative/anxiogenic effects), but left CPP for the immediate effects of cocaine intact (Wenzel et al., 2014). Compared to conditioned reward and habit learning, conditioned withdrawal has been relatively understudied. It remains an exciting and open area for future research.

4.27.4 Conclusion

Associative learning and memory are clearly involved in components of addiction, particularly in relapse. Contexts, cues, and affective states associated with drug use can trigger craving and goal-directed instrumental drug seeking and taking by a positive incentive state or removal of an aversive state. After chronic or repeated use, drug seeking and craving may be driven by learned associations and/or autonomous, habitual cue-conditioned behavior. Additionally, there is a significant overlap between the neurobiology of associative learning and memory and the neurobiology of addiction; they share many molecular substrates and neurocircuits. As a result, current accounts of addiction include aspects of associative learning and memory; research on the neural substrates of drug conditioning now dominate the literature. However, the transition from recreational to pathological and

compulsive drug seeking may involve processes other than associative learning and memory, such as sensitization, allostasis, or loss of inhibitory control. The long-lasting neuroadaptations underlying these components may only partially overlap with those underlying traditional associative learning. Understanding the neurobiology of addiction-related "memories," whether associative or nonassociative, is necessary for development of effective treatments for addiction-related behaviors.

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