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The Nucleus Accumbens: Mechanisms of Addiction across Drug Classes Reflect the Importance of Glutamate Homeostasis

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ABBREVIATIONS: ACh, acetylcholine; AGS, activator of G protein; AMN082, *N*,*N*′-dibenzhydrylethane-1,2-diamine dihydrochloride; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AP5, (2*R*)-amino-5-phosphonovaleric acid; AZD8529, trifluoromethoxy)phenyl]methyl]-3H-isoindol-1-one; BAC, bacterial artificial chromosome; BLA, basolateral amygdala; CAM, cell adhesion molecule; CaMKII, calmodulin-dependent protein kinase II; CB, cannabinoid; CI, Ca^{2+} impermeable; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; CP, Ca^{2+} permeable; CPP, conditioned place preference; CR, conditioned response; CREB, cAMP response element binding protein; CS, conditioned stimulus; DNQX, 6,7-dinitroquinoxaline-2,3-dione; DREADD, designer receptor exclusively activated by designer drugs; eCB, endogenous cannabinoid; ECM, extracellular matrix; EPSC, excitatory postsynaptic current; ERK, extracellular signal–regulated kinase; FR, fixed ratio; GLT, glutamate transporter; GluR, glutamate receptor; HSV, herpes simplex virus; IEG, immediate early gene; ILC, infralimbic cortex; JNJ-16259685, 3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl)-(*cis*-4-methoxycyclohexyl)-methanone; LTD, long-term depression; LTP, long-term potentiation; LY293558, (3*S*,4a*R*,6*R*,8a*R*)-6-[2-(1*H*-tetrazol-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid; LY341495, 2-[(1*S*,2*S*)-2-carboxycyclopropyl]-3-(9*H*-xanthen-9-yl)-D-alanine; LY379268, (1*S*,2*R*,5*R*,6*R*)-2-amino-4-oxabicyclo[3.1.0]-hexane-2,6-dicarboxylic acid; LY404039, (−)-(1*R*,4*S*,5*S*,6*S*)-4-amino-2-sulfonylbicyclo[3.1.0]hexane-4,6-dicarboxylic acid; mAChR, muscarinic acetylcholine receptor; mEPSC, miniature excitatory postsynaptic current; MFZ 10-7, 3-fluoro-5-[2-(6-methyl-2-pyridinyl)ethynyl]benzonitrile hydrochloride; mGluR, metabotropic glutamate receptor; MK-801, [5*R*,10*S*]-[+]-5-methyl-10,11- dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine; MMP, matrix metalloproteinase; MMPIP, 6-(4-methoxyphenyl)-5-methyl-3-pyridin-4-ylisoxazolo[4,5-*c*]pyridin-4(5*H*)-one; MPEP, 2-methyl-6-(phenylethynyl)pyridine; mPFC, medial prefrontal cortex; MSN, medium spiny neuron; MTEP, 3-((2-methyl-4-thiazolyl)ethynyl)pyridine; NAc, nucleus accumbens; NAC, *N*-acetylcysteine; nAChR, nicotinic acetylcholine receptor; NAcore, nucleus accumbens core; NAshell, nucleus accumbens shell; NBQX, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[*f*]quinoxaline-2,3-dion; NMDA, *N*-methyl-D-aspartic acid; NMDAR, *N*-methyl-D-aspartic acid receptor; nNOS, neuronal nitric oxide synthase; NO, nitric oxide; PDE, phosphodiesterase; PFC, prefrontal cortex; PKA, protein kinase A; PLC, prelimbic cortex; PPF, propentofylline; PPR, paired-pulse ratio; PR, progressive ratio; PSD, postsynaptic density protein; PVT, periventricular nucleus of the thalamus; RCT, randomized controlled trial; Ro67-7476 [(2*S*)-2-(4-fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-pyrrolidine; SCH 23390 7-chloro-3-methyl-1-phenyl-1,2,4,5-tetrahydro-3-benzazepin-8-ol; sEPSC, spontaneous excitatory postsynaptic current; sGC, soluble guanylate cyclase; siRNA, small interfering RNA; SKF 82958, 3-allyl-6-chloro-1-phenyl-1,2,4,5-tetrahydro-3-benzazepine-7,8-diol; SYN119, 9H-Xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide; THC, Δ-9-tetrahydrocannabinol; US, unconditioned stimulus; VGlut, vesicular glutamate transporter; vHPC, ventral hippocampus; VP, ventral pallidum; VTA, ventral tegmental area; WIN 55,212-2, (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-napthalenylmethanone; x_c-, cystine-glutamate exchanger.

Abstract——**The nucleus accumbens is a major input structure of the basal ganglia and integrates information from cortical and limbic structures to mediate goal-directed behaviors. Chronic exposure to several classes of drugs of abuse disrupts plasticity in this region, allowing drug-associated cues to engender a pathologic motivation for drug seeking. A number of alterations in glutamatergic transmission occur within the nucleus accumbens after withdrawal from chronic drug exposure. These drug-induced neuroadaptations serve as the molecular basis for relapse vulnerability. In this review, we focus on the role that glutamate signal transduction in the nucleus accumbens plays in addiction-related behaviors. First, we explore the nucleus accumbens, including the cell types and neuronal populations present as well as afferent and efferent connections. Next we discuss rodent models of addiction and assess the viability of these models for testing candidate pharmacotherapies for the prevention of relapse. Then we provide a review of the literature describing how synaptic plasticity in the accumbens is altered after exposure to drugs of abuse and withdrawal and also how pharmacological manipulation of glutamate systems in the accumbens can inhibit drug seeking in the laboratory setting. Finally, we examine results from clinical trials in which pharmacotherapies designed to manipulate glutamate systems have been effective in treating relapse in human patients. Further elucidation of how drugs of abuse alter glutamatergic plasticity within the accumbens will be necessary for the development of new therapeutics for the treatment of addiction across all classes of addictive substances.**

I. Introduction

Drug addiction is a pervasive neuropsychiatric disease that imposes an immense societal cost. Fundamentally, the core behavioral pathology of addiction to any substance is the propensity to relapse, even after periods of extended abstinence. Thus, the primary outcome measure of an effective treatment of addiction is the prevention or reduction of ongoing relapse vulnerability (Vocci and Ling, 2005), yet current pharmacological and behavioral therapies help only a small percentage of addicts achieve enduring relief from relapse. As an example, the most advanced U.S. Food and Drug Administration–approved compound for aiding in the cessation of cigarette smoking is varenicline, which has a relapse rate of approximately 60% after 3 months of treatment (Cahill et al., 2013). Many social theories have been proffered to explain the vulnerability to relapse, from lack of moral will power to the need for social acceptance. However, these sociological explanations have largely proven to be an impediment to developing and employing evidence-based treatment strategies derived from our emerging understanding of the core neuropathological mechanisms underlying drug addiction.

To begin our review, we operationally define relapse vulnerability as the inability to manage the motivation to use drugs. In other words, situations, environmental stimuli, or interoceptive mental states previously associated with a drug initiate a desire to seek, obtain, and use drugs that supersedes consideration of the negative consequences. Under these circumstances, it is nearly impossible to regulate or amend motivated behaviors related to drug seeking and drug use. The neurobiological processes used for amending behavior to reduce possible negative outcomes can be collectively described as "top-down control" and are harbored, at least in part, in glutamatergic projections to the striatum that arise from neurons in the prefrontal cortex (PFC), as well as allocortical regions such as the amygdala and hippocampus. In particular, glutamatergic projections to the nucleus accumbens (NAc) serve as a critical portal, whereby analyses of environmental contingencies are communicated to the basal ganglia to shape adaptive behavioral responding. Therefore, consonant with the impaired ability of drug-dependent individuals to regulate drug seeking, the search to understand the neurobiology of relapse has developed a strong focus on how drug use affects plasticity of neuronal communication in the NAc. Although we incorporate neurobiological information derived from many models of addiction, because of the focus on relapse and involvement of glutamatergic inputs to the NAc, we bring the strongest focus to preclinical data generated using the self-administration model of drug use.

In this review, we begin by cataloging various animal models of addiction (section II). Then, we describe the cellular composition of the NAc and its connectivity with other brain regions (sections III and IV). Next we catalog and evaluate the neuroadaptive changes in the accumbens produced by addictive drugs (section V). Finally, we describe the pharmacological and chemogenetic manipulations that reverse maladaptive neuroadaptations and inhibit drug seeking in both the laboratory (section VI) and clinic (section VII).

II. Modeling Addiction and Relapse in the Laboratory Setting

Animal models have become useful tools in advancing our understanding of neurobiological processes underlying the initiation, maintenance, compulsive use, and relapse to drug use in human drug addiction. Compared with human studies, animal models allow more invasive and precise experiments that employ a more controlled and less expensive analysis of the biology of addiction (Domjan, 2003; Markou et al., 2009). However, the potential value of using laboratory animals in studying human personality traits and cognitive neuropsychiatric disorders is limited (Gosling, 2001). Below we review the most commonly used animal models in addiction research, and we provide an analysis of their relative utility for studying addiction-associated synaptic plasticity at glutamatergic synapses in the NAc and the vulnerability to relapse.

A. What Are We Trying to Model in Experimental Animals?

Animal models are the most efficient method for determining how gene expression and cell signaling in specific brain circuits mediate learning and memory as well as the expression of motivated behavior based on learned associations. However, when we are extrapolating to a behavioral disorder that is defined in part by uniquely human criteria, it is important to accept the limitations of animal models. Models of addiction have evolved over the last 2 decades to provide increasing face validity through anthropomorphizing rodent behavior (Piazza and Deroche-Gamonet, 2014) but have been less successful at producing predictive validity in terms of drug development. However, the use of anthropomorphic models of addiction has produced procedures that yield behaviors that appear similar to certain human addiction endophenotypes, such as impulsivity, escalating drug use, intrusive thinking, or compulsive drug seeking (Ahmed et al., 2002; Everitt et al., 2008; Perry and Carroll, 2008; Dalley et al., 2011; Chen et al., 2013). However, below we argue that there are limits in extrapolating from rodent to human behavior and that modeling shared neurobiological processes that are similarly altered by addictive drugs may be the most useful approach.

To encapsulate both glutamatergic physiology and the relevance of various animal models of addiction, below we focus on models that have successfully revealed involvement of the circuitry providing glutamatergic synapses to the NAc. In particular, we focus on the innervations arising from cortical regions, such as the prelimbic cortex (PLC) and infralimbic cortex (IFC) in rodents and the anterior cingulate and subgenual PFC in humans, and allocortical regions, such as the basolateral amygdala (BLA) and ventral hippocampus in both humans and rodents (Fig. 1). As indicated above, the focus on these synapses arises from their role in a defining characteristic of addiction—namely, a failure to suppress the overwhelming motivation to relapse to drug use.

B. Using Animal Models to Understand Constitutive and Transient Adaptations

In applying animal models of addiction toward understanding the neurobiology of the addicted state, investigators are asking two fundamental questions: 1) What are the long-lasting, constitutive changes produced by addictive drugs that may constitute the addiction? 2) What are the transient neurologic processes that mediate the expression of behavioral pathology? Although animal models are behaviorally defined by the expression of the behavioral effects of a drug (e.g., behavioral sensitization or drug seeking), the neurobiological analyses are largely made after a period of withdrawal or abstinence. In other words, animal models have focused on the second question in terms of behavior and the first question in terms of understanding addiction neurobiology. We will reflect on this disconnect as we proceed to analyze each model in terms of value in answering both questions.

C. Motor Sensitization

Sensitization occurs when repeated exposure to a stimulus augments a behavioral or physiologic response compared with the first stimulus presentation. In terms of drugs of abuse, cocaine, amphetamines, nicotine, ethanol, morphine, and Δ-9-tetrahydrocannabinol (THC) have all been shown to produce sensitization of locomotor behavior in animal models (Vezina and Stewart, 1989; Borowsky and Kuhn, 1991; Paulson and Robinson, 1995; Cadoni and Di Chiara, 2000; Cadoni et al., 2001; Quadros et al., 2002). Sensitization is most commonly assayed by measuring increases in locomotor activity after repeated experimenter-administered (noncontingent) drug delivery. Although a single drug injection may be sufficient to elicit behavioral sensitization lasting a few days (Post and Weiss, 1988; Valjent et al., 2010), repeated drug administration more generally appears necessary to produce enduring (weeks to months) sensitization. In rodent models of sensitization, augmented behavior to an acute drug challenge is reliably paralleled by enhanced dopaminergic activity in the NAc (Kalivas and Duffy, 1990; Johnson and Glick, 1993; Paulson and Robinson, 1995; Cadoni and Di Chiara, 2000) (with the possible exception of alcohol; see Zapata et al., 2006). In contrast with dopamine, repeated noncontingent drug exposure variably decreases basal levels of extracellular glutamate in the NAc in the case of cocaine or has no effect in the case of amphetamine (Pierce et al., 1996; Xue et al., 1996). In addition, when behavioral sensitization is expressed by a subsequent noncontingent drug injection, there is an increase in nucleus accumbens core (NAcore) extracellular glutamate that

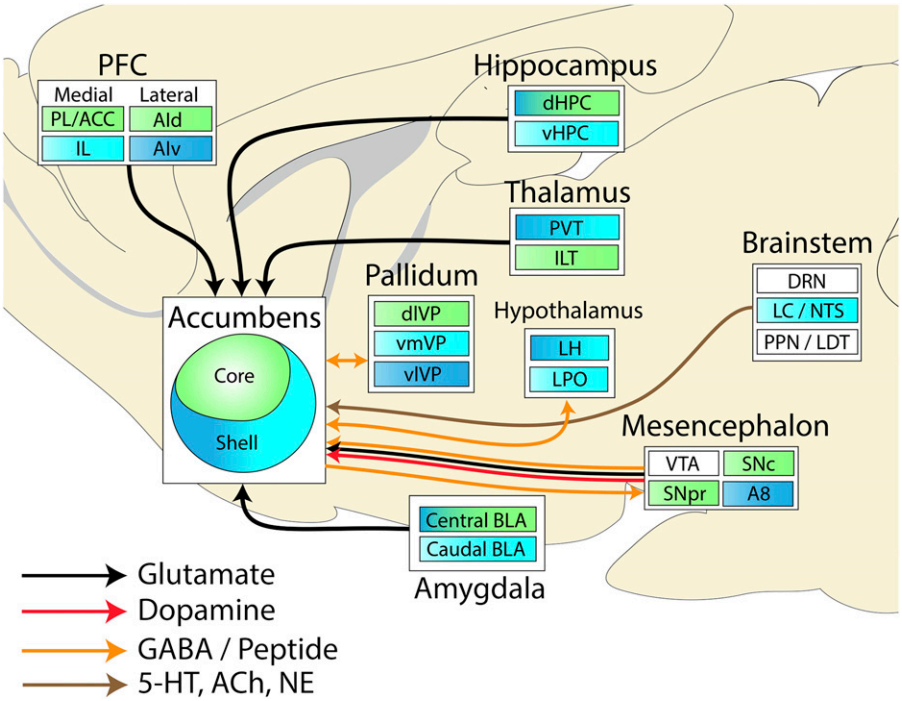

Fig. 1. NAc connectivity. The NAc receives inputs from cortical, allocortical, thalamic, midbrain, and brainstem structures. In turn, it sends projections to other basal ganglia nuclei (VP and substantia nigra pars reticulata), nuclei in the mesencephalon, the hypothalamus, and the extended amygdala. Note that many structures project from different subareas to the NAcore or NAshell. For clarity, these projections have been color coded as projecting to the NAcore (green), medial NAshell (light blue), or lateral NAshell (dark blue); in reality, many regions project to both the NAcore and NAshell along topographical gradients (e.g., dorsoventral projections from the hippocampus terminating from lateral to medial parts of the accumbens; shown as color gradients in the figure). A number of regions project uniformly throughout the accumbens and are marked white. A8, retrorubral area; ACC, anterior cingulate cortex; AId, dorsal anterior insular; AIv, ventral anterior insular; dHPC, dorsal hippocampus; dlVP, dorsolateral ventral pallidum; DRN, dorsal raphe nucleus; IL, infralimbic cortex; ILT, interlaminar nuclei of the thalamus; LC, locus coeruleus; LH, lateral hypothalamus; LPO, lateral preoptic area; NTS, nucleus of the solitary tract; PL, prelimbic cortex; PPN, pedunculopontine nucleus; PVT, paraventricular nucleus of the thalamus; vlVP, ventrolateral ventral pallidum; vmVP, ventromedial ventral pallidum; SNc, substantia nigra pars compacta; SNpr, substantia nigra pars reticulata.

depends on the presence of environmental cues associated with previous drug exposure and occurs only in rats that actually show a sensitized behavioral response (Bell et al., 2000; Hotsenpiller et al., 2001). This linkage between glutamate release and learned drug–environment associations is manifested less with dopamine, in which the extracellular levels are elevated as part of the acute pharmacological action of the drug, although drug–environment associations can augment the drug-induced increase in extracellular dopamine (Badiani et al., 1995; Bell et al., 2000). Importantly, in humans and nonhuman primates, elevated dopamine appears to be more dependent on the presence of a drug-associated context or cues (Bradberry, 2007; Narendran and Martinez, 2008; Vezina and Leyton, 2009).

In parallel with the basal levels of extracellular glutamate being variably altered by a behavioral sensitizing treatment protocol depending on the addictive drug, glutamate receptor (GluR) levels in the accumbens also vary depending on the drug being used. Notably, whereas repeated cocaine administration elicits a time-dependent increase in surface expression of the GluR1 subunit of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors that is present after at least 1 week but not on day 1 of withdrawal, a sensitizing treatment regimen of morphine or amphetamine does not consistently alter the level of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) or *N*-methyl-D-aspartic acid receptor (NMDAR) subunits (Boudreau and Wolf, 2005; Boudreau et al., 2007; Kourrich et al., 2007; Ghasemzadeh et al., 2009; Ferrario et al., 2011). The changes produced by repeated cocaine on GluR1 levels are paralleled by enduring increases in AMPA currents, which are quantified as the AMPA/*N*-methyl-D-aspartic acid (NMDA) ratio and the density of dendritic spines in accumbens medium spiny neurons (MSNs) (Thomas et al., 2001, 2008; Norrholm et al., 2003; Robinson and Kolb, 2004; Kourrich et al., 2007; Shen et al., 2009; Dietz et al., 2012). However, the increase in spine density does not occur after daily noncontingent administration of morphine (Robinson and Kolb, 1999). The morphologic component of drug-induced plasticity is discussed in greater detail in section V below.

In summary, although substantial face validity of behavioral sensitization is lost because the drug is experimenter administered, the administration protocol induces some forms of plasticity at glutamatergic synapses. However, the most replicable effects of

noncontingent drug administration in the sensitization model, regardless of the addictive drug, are on dopamine neurons in the ventral tegmental area (VTA) and in releasing dopamine in the NAc (Kalivas and Stewart, 1991; Jones and Bonci, 2005). Thus, many investigators have used a variety of addictive drugs and stress to show that the initiation (development) of sensitization by repeated drug injection depends on adaptations in excitatory and peptidergic afferents to the VTA and transient changes in glutamate synaptic strength on dopamine neurons (Bonci and Borgland, 2009; Lüscher and Malenka, 2011). In addition, the majority of studies show that the expression of locomotor sensitization is associated with sensitized release of dopamine in the accumbens (Steketee and Kalivas, 2011). In contrast with dopamine, behavioral sensitization is not as consistently associated with drug-induced changes in glutamate transmission in the accumbens, as discussed above. Not only do different classes of drugs producing behavioral sensitization elicit distinct enduring changes in AMPARs and spine morphology in accumbens MSNs, but there is also a requirement for contextual associations with the drug in developing and expressing glutamate release and synaptic plasticity. Although the expression of sensitized drug-induced locomotion can be conditioned to and made dependent on contextual cues (Stewart, 1991; Crombag et al., 2000), it is also clear that behavioral sensitization can be induced without associating the unconditioned motor response with a conditioning stimulus or context. This is perhaps most clearly demonstrated by the fact that intra-VTA injections of amphetamine do not elicit an unconditioned locomotor response, whereas they do induce enduring locomotor sensitization to a subsequent systemic or intra-accumbens injection of amphetamine or cocaine (Kalivas and Weber, 1988; Vezina, 1993). Taken together, these data indicate that although drug-induced dopamine release sensitizes in parallel with behavior, it is necessary to develop learned associations between the unconditioned drug response and contextual or discrete environmental cues in order to engage the cortical and allocortical inputs to the accumbens (Fig. 1) with noncontingent injections. Unfortunately, most studies have not carefully controlled learned associations made with noncontingent drug effects, resulting in the sensitization literature identifying variable levels of behavior and glutamatergic adaptations. Another important confound of sensitization, with the exception of a few studies regarding contextual cues (Badiani et al., 1995; Uslaner et al., 2001), is that the majority of studies on the expression of sensitization rely on an acute drug injection to elicit the behavior. Accordingly, the distinct acute pharmacology of each class of drug can produce reversible changes that may confound or mask measures of glutamate transmission contributing to the sensitized behavioral response. In addition to the confounding acute effects of the drug, the face validity of the sensitization model is also limited by the fact that a sensitized dopamine response is largely absent in monkeys and humans with high levels of cumulative exposure (Bradberry, 2007).

D. Conditioned Place Preference

The marked and variable effect of learned associations on behavioral and cellular measures in the behavioral sensitization paradigm is better controlled in the conditioned place preference (CPP) protocol (Tzschentke, 2007). CPP is a simple form of classic conditioning or Pavlovian conditioning, a learning process that involves either positive or negative associations between two stimuli. In either case, a conditioned stimulus (CS) or a previously neutral stimulus that does not elicit a response gains predictive value over the occurrence of an unconditioned stimulus (US) (e.g., acute experimenter-delivered drug injection) through training. The CPP procedure generally consists of three phases: habituation, conditioning, and testing. During habituation, the animal is allowed to move freely throughout a test apparatus that is most often of a two-chamber or three-chamber construction. At this time, initial preference is measured and the researcher may assign treatment pairings in a biased or unbiased design, a choice that can affect the final results. In an unbiased design, subjects are randomly assigned regardless of their initial preferences. In a biased design, the initially nonpreferred side is paired with the test drug. During conditioning, one chamber of the apparatus is paired with the drug, whereas the other side is paired with vehicle injection. This training involves multiple pairings of each contextually distinct compartment with the drug or vehicle over a period of several days, but protocols vary in the number and schedule of pairings. After training, preference is tested in a drug-free state by measuring the amount of time spent in each chamber. The choice of one context over the other is said to impart information regarding the drug-induced motivational state. If the drug is "rewarding," the subject is expected to spend more time in the drug-paired environment, thus producing CPP (Bardo and Bevins, 2000). Conversely, if the drug induces a negative state, the subject will avoid the paired context, producing a place aversion (Mucha et al., 1982).

Under the correct conditions, cocaine, amphetamines, ethanol, and morphine have all been shown to produce a CPP (Tzschentke, 2007). Recently, place preference for amphetamines was demonstrated in humans (Childs and de Wit, 2009). Early research suggested an involvement of D1 dopamine receptors and NMDA-type glutamate receptors in the establishment of cocaine CPP, whereas the AMPA-type glutamate receptors seem to be involved in CPP expression as elucidated by using systemic delivery of specific AMPA and NMDA inhibitors (Cervo and Samanin, 1995). However, either

the AMPA/kainate antagonist 6,7-dinitroquinoxaline-2,3-dione (DNQX) or the D1/D2 dopamine antagonist fluphenazine delivered directly to the accumbens reduces CPP expression, whereas only DNQX affects acquisition in rats trained with cocaine (Kaddis et al., 1995). Similarly, methamphetamine CPP is attenuated by intracerebroventricular pretreatment with the antagonist at GluN2B containing NMDA channels ifenprodil, DNQX, or the metabotropic glutamate receptor (mGluR) 5 negative allosteric modulator 2-methyl-6-(phenylethynyl)pyridine (MPEP) during pairing (Miyatake et al., 2005). These data indicate that glutamatergic activity may be crucial for learning the association between environmental stimuli and drug reward and identify a locus of action in the mesoaccumbens pathway (see section VI for more detailed pharmacology of glutamate receptors in CPP).

CPP can be also be extinguished, and reinstatement can be measured as a proxy of drug craving and relapse (Mueller and Stewart, 2000). Extinction is facilitated by repeatedly administering vehicle injections in both compartments or conducting repeated preference testing until preference is extinguished. Extinguished CPP can be reinstated with a drug-priming injection (or in some cases, stress). A role for glutamatergic transmission has been demonstrated in CPP reinstatement. For instance, NMDAR antagonists have been used to suppress cocaine- and morphine-primed reinstatement of place preference (Ribeiro Do Couto et al., 2005; Maldonado et al., 2007). Many of the results obtained using the CPP reinstatement procedure are complementary with self-administration studies (see below), but these models evaluate different aspects of reward (conditioned approach versus operant responding); thus, the findings are not always consistent. For example, although memantine (an NMDA antagonist) reduced reinstatement of cocaine CPP, it did not block cocaine-primed reinstatement in the operant task. The drug did, however, abolish lever discrimination by increasing inactive lever responses (Bespalov et al., 2000; Maldonado et al., 2007).

The CPP paradigm is a popular drug-screening tool in animal models because it is an inexpensive and efficient procedure. Moreover, with the addition of a reinstatement test in many studies, the CPP paradigm is useful to evaluate both the development and expression of drug-induced behavioral and neurologic adaptations. However, reinstating CPP is usually accomplished by acute readministration of the drug since the conditioned context has been extinguished and, as discussed above, the acute drug pharmacology may interfere with the fidelity of measures of glutamatergic transmission relevant to addiction. From the perspective of engaging cortical and allocortical inputs to the NAc, the conditioned associations activated in CPP likely lead to activation of this circuit in the process of recalling learned information to guide behavior. Although this has not been directly evaluated at the level of extracellular glutamate levels, daily noncontingent cocaine injections using a CPP protocol produce enduring increases in dendritic spine density in accumbens MSNs (Pulipparacharuvil et al., 2008; see the discussion on morphologic plasticity in section V). In conclusion, although it involves noncontingent drug administration, this protocol is appropriate for consistently engaging cortical and allocortical afferents to the accumbens because of the requirement for a learned contextual association to express CPP. Because the expression of context-induced place preference is drug free, it is possible to perform studies quantifying changes in glutamatergic plasticity or transmission initiated by the drug-paired context. As an example, changes in synaptic AMPAR expression were observed in the hippocampus when animals were re-exposed to a morphine-paired context, even if they received a saline injection (Xia et al., 2011). Furthermore, morphine CPP also increased basal synaptic transmission, altered synaptic levels of NMDAR subunits, and inhibited hippocampal long-term potentiation (LTP) (Portugal et al., 2014). Although the CPP protocol has drawbacks in terms of requiring drug-induced reinstatement, it is useful for determining the neural plasticity associated with drug-induced learned behavior. Indeed, in transgenic mouse models in which establishing self-administration is technically challenging, CPP has been the choice of noncontingent drug treatment paradigms to evaluate addiction-associated neuroadaptations (Russo et al., 2010). However, even using transgenic mice, the literature is gradually moving from CPP to self-administration models of addiction because of the latter's greater face validity with human addiction. It is also unclear whether CPP is isomorphic with drug self-administration, because some drug classes elicit one drug-related behavior but not the other (Bardo and Bevins, 2000).

E. Self-Administration

More complex animal models of drug addiction are based on the analysis of behavioral output using schedules of reinforcement, established by Ferster and Skinner (1957). Instrumental behavior occurs because it was previously involved in producing certain consequences (Weeks, 1962; Schuster and Thompson, 1969; Domjan, 2003). Modern approaches to studying instrumental conditioning in drug addiction include operant responses (e.g., a lever press or nose poke on an opperandum) that lead to the delivery of an US (e.g., an intravenous drug infusion). This procedure of positive reinforcement is termed *self-administration*. Self-administration is frequently used to model addiction because it more closely resembles the human condition compared with an experimenter-delivered drug. In self-administration models, animals are placed in operant chambers, and completion of a schedule of reinforcement via lever presses or nose pokes is accompanied by intravenous or oral drug delivery. Usually, fixed-ratio

(FR) schedules are used in self-administration models, such that an animal is required to press a lever a fixed number of times prior to drug delivery. Alternatively, progressive-ratio (PR) schedules are used to examine the reinforcing efficacy of a drug (or the probability that a drug will serve as a reinforcer). In a PR schedule, an animal must produce an increasing number of responses on an opperandum for each successive reinforcer. The self-administration model can be used to model various components of human drug use, including learning to take the drug (acquisition), stable regular drug use (maintenance), progressively increasing and compulsive drug use (escalation), drug abstinence (withdrawal with or without extinction of responding for the drug), and relapse to drug seeking (reinstated or context-induced responding).

1. Acquisition. In the absence of external influences, only a subset of animals will acquire operant self-administration of drugs of abuse, confirming that individual differences exist in risk vulnerability to drug abuse. Intrinsic (e.g., age, sex, trait, or genetics) and extrinsic (e.g., stress) factors will influence individual differences in the rate of acquisition or percentage to reach preset criteria (Bardo et al., 2013). For example, impulsivity is a trait that can act as both a determinant and a consequence of drug use (de Wit, 2009). Impulsivity may be a risk factor during initiation of recreational drug use, as well as during dysregulated increasing intake of and relapse to drug use in a spiral of addiction (Poulos et al., 1995; Winstanley et al., 2010). As such, impulsivity may be an important endophenotype for addiction pathology (Ersche et al., 2011). Research on both the clinical and preclinical levels of analysis examining the neurobiological underpinnings of impulsivity has implicated main structures in the corticostriatal pathway, including the PFC, orbitofrontal cortex, BLA, and the NAc (Dalley et al., 2011).

Procedures have been developed to examine the acquisition stage of addiction such that an animal is exposed to the contingencies associated with an active lever. In other words, responses on an active lever will result in the presentation of a reinforcer (e.g., food or drug), and an inactive lever will yield no programmed consequence. Using this procedure, differences in acquisition of drug self-administration can be measured. To model acquisition of drug use, Carroll and Lac (1993) developed an autoshaping procedure in which the active lever is extended on a fixed time schedule. The active lever will extend to indicate that a drug infusion is available contingent on a lever press every 60 seconds, and a lever press will deliver this drug infusion along with the illumination of a CS (a cue light above the lever; Carroll and Lac, 1993). If no lever press occurs within 15 seconds, a drug infusion plus a CS (cue light) will occur noncontingently to aid in the acquisition of a Pavlovian association between the CS and the drug infusion (a US). The NAcore was found to be involved in acquisition of instrumental responses, because lesions to this area inhibit autoshaped response performance (Cardinal et al., 2002) and disrupt Pavlovian-instrumental transfer, which is the facilitation of instrumental responses by the presentation of a CS (Hall et al., 2001; Leung and Balleine, 2013).

Using autoshaping procedures, it was observed that some animals tend to preferentially approach and interact with stimuli that predict the delivery of reward (Brown and Jenkins, 1968). Literature on learning and incentive salience has shown that a CS will elicit individual differences in conditioned responses (CRs), such that some animals will exhibit sign-tracking behavior. These animals tend to approach the discrete stimulus associated with the reward (e.g., the lever or light), whereas goal-tracking behavior is defined as the tendency to approach the goal (e.g., the food receptacle) (Silva et al., 1992; Flagel et al., 2008). Individual differences in CRs predict novelty-seeking behavior and acquisition of cocaine self-administration in rats, such that sign trackers display greater novelty-seeking behavior and faster acquisition of cocaine self-administration (Robinson and Flagel, 2009; Beckmann et al., 2011). Interestingly, differential and region-specific phasic glutamate signaling has been found in the NAcore and the PLC during sign-tracking behavior to a reward-predictive stimulus within Pavlovian conditioned approach behavior. Phasic glutamate signals in the NAcore were slower and bimodal, with peaks differentially associated with the type of stimulus presented (lever versus food), whereas phasic glutamate signals within the PLC were faster and elicited only by food presentation. Finally, no glutamate release was elicited by stimuli not paired with food in either brain region. Thus, glutamate dynamics may play an important role in stimulus-reward learning and incentive salience attribution (Beckmann et al., 2014).

2. Maintenance. Drug self-administration initially involves action-outcome learning fueled by incentive value of the drug (goal-directed behavior) and is believed to then transition to habit formation elicited by stimuli that have taken on associative value. This is thought to underlie drug-seeking motivation (Everitt and Robbins, 2005; Hogarth et al., 2013). Once self-administration is established (typically on a FR schedule of reinforcement), continued intake can be measured or manipulated via administration of pharmacological compounds that might increase or decrease drug intake. Dose-response curves can be generated using these procedures (e.g., 1 or 2 hours of access to drug self-administration per day).

PR schedules were initially developed as a means for evaluating the rewarding properties of sweetened-milk solutions in rodents (Hodos, 1961). As described above, the PR is used to determine the reinforcing efficacy of a substance by increasing the response requirements

during self-administration until the performance of the animal falls below an established criterion (Richardson and Roberts, 1996). Using this technique, the investigator can determine the maximum amount of effort that will support self-administration behavior, commonly referred to as the "break point." PR experiments have been used with great success with psychomotor stimulants because the break point can be assessed in a single behavioral session and is dose dependent (Arnold and Roberts, 1997). Interestingly, unlike FR experiments, PR experiments and break point values are heavily influenced by the estrus cycle (Roberts et al., 1989); with the ongoing emphasis on the inclusion of female subjects in addiction studies, cycle data must be collected to properly interpret results from PR studies using female subjects. Furthermore, opiates and sedative drugs may not be well suited for the PR experimental design. Despite the fact that rats are highly motivated to seek heroin during self-administration, PR analyses show that motivation appears to decrease with each subsequent drug infusion; as such, dose-response relationships were not able to be generated by using a PR schedule (Roberts and Bennett, 1993).

3. Escalation. Although limited-access procedures model the maintenance of drug use, it has been postulated that drug addiction results in an escalating, dysregulated spiral such that intake continues to increase. The escalation procedure was designed to model this dysregulated intake, and it typically results in increasing intake of a drug across sessions (Ahmed and Koob, 1998, 1999, 2004, 2005). In this paradigm, animals are given extended access to self-administer a drug (e.g., 6 hours of drug self-administration per day), and drug infusions are measured. With stimulants such as cocaine (Ahmed and Koob, 2004), D-amphetamine (Gipson and Bardo, 2009), methylphenidate (Marusich et al., 2010), and methamphetamine (Kitamura et al., 2006), it has been well established that animals escalate drug intake across sessions. In addition, animals given extended access to heroin have shown escalation behavior (Ahmed et al., 2000) compared with limited-access groups, which show relatively stable levels of intake across sessions. It should be noted, however, that achieving escalation of nicotine self-administration is difficult, although not impossible (one study used an intermittent access schedule and achieved escalation; Cohen et al., 2012). Although it was more recently shown that escalated intake involves other processes such as learning and stimulus control (Beckmann et al., 2012), this model has been used extensively to examine the neurobiological changes that are specific to dysregulated, increased intake. For example, intracranial self-stimulation thresholds increase after escalated intake (Ahmed et al., 2002). During escalation, the brain is hypothesized to achieve "allostasis," in which it re-establishes stability after chronic drug use (Koob, 2004). The change from voluntary, goal-directed drug use to uncontrolled, compulsive drug use is the result of a neurobiological change in control from the PFC to the striatum (Kalivas and Volkow, 2005). The NAc has been described as a "gateway" in the transition from limbic to motor control in the addiction cycle (Kalivas, 2009); in this transition, cortical and allocortical glutamatergic projections to the striatum come to play a necessary role in motivated behavior. It has also been shown that there is a shift from the ventral to dorsal striatum during the transition from goal-directed drug taking to more habitual, compulsive drug-taking behavior (Everitt and Robbins, 2005, 2016).

4. Abstinence. Preclinical animal models of abstinence consist of two variations: those that employ extinction training, and those that employ abstinence without extinction training. During extinction, the levers are extended during daily sessions, but responses to either lever result in no programmed consequence, thus extinguishing the responding on the drug-paired lever. Extinction training is a form of new learning in which new contingencies are established between the behavioral response and the outcome. In this way, an animal learns to withhold (inhibit) lever pressing. In this process, the previously drug-paired context becomes a context associated with extinction. In contrast, forced abstinence involves leaving the animal in his or her home cage for a specified period of time after drug administration. Some hypothesize that the neuroadaptations that occur during abstinence from drugs are compensatory mechanisms that are opposite from what occurred during drug use (the opponent-process theory of motivation, proposed by Solomon and Corbit, 1974) and may underlie the switch from drug use to drug addiction (Koob et al., 2004). Although dependence and withdrawal have long been defined as hallmarks of addiction, it is now recognized that these symptoms alone, without compulsion, are neither necessary nor sufficient for addiction (O'Brien, 1997; Hyman et al., 2006). It has also been postulated that bouts of abstinence may lead to increased impulsivity, and this leads to increased relapse vulnerability (Winstanley et al., 2010). Interestingly, extinction training during abstinence, rather than abstinence alone, seems to be necessary to engage the PLC-NAcore circuit in cocaine-seeking behavior, because inhibition of the PLC does not inhibit reinstatement when animals are placed back into the environment previously associated with cocaine after forced abstinence (Fuchs et al., 2006; Knackstedt et al., 2010b). Extended periods of abstinence without extinction training, however, have been shown to lead to an "incubation" of cocaine craving such that animals press the active lever to receive cues previously paired with a drug of abuse, and this is associated with an increase in calcium-permeable AMPARs (Grimm et al., 2001; Shaham et al., 2003; Conrad et al., 2008; see section V for a more in-depth discussion of this phenomenon). More recently, punishment models/devaluation have been used

to inhibit drug responding prior to reinstatement testing (see below).

5. Relapse. In preclinical animal models, relapse of drug seeking is modeled using the reinstatement paradigm. Animals are trained to self-administer a drug; after response stability (indicating acquisition of drug self-administration), animals enter abstinence with or without extinction. With new contingencies in place (lever presses lead to no programmed consequence), animals will learn to inhibit the prepotent response to press the lever. Then, after response stability in extinction or after a specified period of abstinence, animals are given a priming stimulus to initiate drug-seeking behavior. There are several priming stimuli used to elicit motivated behavior in reinstatement models, including 1) a noncontingent priming injection of the previously self-administered drug (this is given systemically in the typical paradigm); 2) a discrete Pavlovian cue (a CS) previously associated with the delivery of a drug infusion; 3) a pharmacological or physical stressor, such as yohimbine or foot shock, respectively; or 4) placement back into the context in which the animal learned to self-administer the drug. In contextual renewal (the fourth paradigm), animals are trained in one context (context A) and learn to associate a constellation of environmental stimuli with drug infusions. Animals are then extinguished to the cues associated with the drug (or just given extinction training with no consequence) in another distinct context (context B), and they are subsequently placed back into context A during reinstatement testing (termed the ABA renewal paradigm; Bouton and Bolles, 1979; Crombag and Shaham, 2002; Shalev et al., 2002; Crombag et al., 2008).

As discussed above, the role of the corticostriatopallidal neural circuitry in reinstated drug seeking has been examined extensively. In general, two subcircuits have been identified as being either limbic [ventral PFC, amygdala, nucleus accumbens shell (NAshell), medial ventral pallidum [VP], and VTA] or motor (dorsolateral PFC, NAcore, dorsolateral VP, and substantia nigra] (Fig. 1) (McFarland and Kalivas, 2001). The limbic subcircuit is most often associated with inducing motivated states that can initiate behavior (e.g., craving and relapse) or can inhibit behavior (e.g., extinguished responding) (Kelley, 2004; Peters et al., 2009). In contrast, the motor subcircuit is involved in expressing motivated behaviors and in the long-lasting compulsive or automatic responses that constitute relapse (Everitt et al., 2008; Kalivas, 2009).

6. Punishment Models. Because one of the hallmarks of addiction is continued drug seeking in the face of adverse effects and because the face validity of forced extinction training has been questioned, researchers have turned to punishment models of response suppression or resistance to suppression (Vanderschuren and Everitt, 2004). Over a decade ago, Deroche-Gamonet et al. (2004) characterized "addict-like" rats upon the basis of meeting three *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition) criteria for addiction, including continued use despite harmful consequences (drug delivery coincident with shock), difficulty stopping drug use (nose pokes during drug-unavailable periods), and high motivation to take the drug (PR break point). Only 17% of rats met criteria for being "addict like" and this behavior emerged only after prolonged drug access. These addict-like rats are shown to have long-lasting deficits in NMDAR-dependent long-term depression (LTD) in the NAcore and mGluR2/3-dependent LTD in the prelimbic PFC compared with nonaddicted rats (Kasanetz et al., 2010, 2013). Relapse-vulnerable rats also show reduced striatal expression of a number of genes encoding synaptic plasticity-related proteins (Brown et al., 2011a). Since the original reports by Everitt and Piazza (Deroche-Gamonet et al., 2004; Pelloux et al., 2007), a number of researchers have adopted the punishment model usually after training under a seek-take chain of reinforcement. Perhaps the most significant findings in this regard are that prolonged cocaine self-administration decreases excitability in the PLC in punishment-resistant, compulsive drug-seeking rats, and optogenetic stimulation of the PLC decreases compulsive drug seeking (Chen et al., 2013). Confirming this inhibitory role for the corticoaccumbens projections, a rat model of inhibitory control showed that the ability to suppress cocaine self-administration depends on activity in the prelimbic PFC (Mihindou et al., 2013).

7. Summary. Although preclinical investigators debate the validity of the different models of relapse, without a doubt, the self-administration/withdrawal/drug-seeking model is the most widely employed because of its face validity with human relapse to drug use. This is primarily because the model involves the contingent administration of the addictive drug, the relapse event occurs even after long periods of withdrawal, and components of stimuli that initiate relapse in humans can be modeled (e.g., discrete and contextual cues or stress). Importantly, refinements continue to increase model face validity and over the last decade have notably involved the incorporation of escalating drug intake and some form of punished responding to further model the compulsive nature of drug use and relapse. However, the increasing face validity of these more recent models must be balanced in part by decreased efficiency, which becomes an important factor in generating animals for subsequent ex vivo postmortem neurobiological measurements or screening potential pharmacotherapies. Thus, the longer drug treatment periods and/or isolation of a subpopulation of animals continuing to use drugs in the presence of punishment markedly decrease the efficiency of obtaining sufficient animals for biologic evaluation. Furthermore, regardless of refinements, there remains considerable debate over the construct validity of the

self-administration/reinstatement model (Epstein et al., 2006). Construct validity is defined as the ability of a model to measure what it claims to measure (in this case, human relapse to use of addictive drugs). Examples of construct validity in the variants of reinstated drug-seeking rats are abundant and include the use of extinction training to reduce lever pressing in withdrawal. While extinction is important for isolating how different environmental factors can reinstate lever pressing, it occurs because the drug is no longer available; in humans, drug cessation attempts result from a complex array of choices in which the negative consequences of continuing to use drugs outweigh the reinforcing consequences. In addition, relapse in humans does not typically follow exposure to the types of drug-priming and cue-induced reinstatement contingencies employed in the model, and the modalities of stress employed in animals, such as footshock or yohimbine injection, are not encountered by humans. Finally, risk of relapse appears to decrease with extended abstinence in humans (Gilpin et al., 1997; Higgins et al., 2000; Dennis et al., 2007), whereas the magnitude of reinstatement in the incubation model does not decrease over time (in fact, it increases with extended periods of abstinence; Grimm et al., 2001; Conrad et al., 2008).

Despite the problems outlined above with construct validity of the various drug-seeking models after drug self-administration, it remains the best model of relapse by incorporating three key features of construct validity. First, in parallel with human use, drugs are self-administered and learned associations are formed between the environment and drug use. Second, neurologic changes produced by drug use that exist after weeks to months of withdrawal are most likely to underpin the enduring nature of relapse vulnerability in human addiction. Finally, by definition, all addictive drugs share vulnerability to relapse; thus, shared neurologic adaptations between drugs in preclinical models that are not shared with natural reinforcers, such as sucrose, can distinguish the neurobiology of conditioned responding for the drug from responding for nonaddictive natural rewards.

Using various versions of the self-administration/relapse model, preclinical scientists have generated abundant data regarding involvement of the cortical and allocortical glutamate transmission in the accumbens in relapse. Accordingly, in this review, we rely entirely on data generated using the self-administration paradigm followed by withdrawal. Where there is not consistency in data between studies, we explore how procedural differences in the paradigm (e.g., the presence or absence of extinction training or the modality used to reinstate behavior) may contribute to distinctions in neurobiological changes. Finally, where data exist, we will attempt to isolate similarities in neurologic adaptations that are shared by different chemical classes of drugs, based on the construct validity that all classes of addictive drugs share vulnerability to relapse as a behavioral definition of the disease and that the shared neurologic adaptations may therefore be more likely to underpin relapse.

III. Nucleus Accumbens: Composition

A. Medium Spiny Neurons

The principle cell type in the striatum is the GABAergic MSN, which comprises approximately 90%–95% of the total neuronal population (Fig. 2). These cells can be subdivided into two distinct subpopulations based on characteristic dopamine receptor (D1/D2) and neuropeptide expression profiles (Gerfen and Surmeier, 2011). D1 receptor–containing MSNs coexpress dynorphin, substance P, and M4 cholinergic receptors, whereas D2 MSNs express enkephalin, neurotensin, and A2a adenosine receptors (Le Moine and Bloch, 1995; Lobo et al., 2006). Dopamine receptors on MSNs are G protein–coupled receptors with largely opposing effects on intracellular signaling cascades, leading to differential responses to dopamine and imbuing the separate cell populations with distinct physiologic properties. D1-type dopamine receptors are coupled to the $G\alpha_{s/olf}$ family of G proteins that activate adenylyl cyclase to stimulate cAMP production and activation of downstream signaling cascades via cAMP-dependent protein kinase and other cAMP-dependent proteins, which ultimately regulate gene expression via transcription factors including cAMP response element binding protein (CREB) (Beaulieu and Gainetdinov, 2011). The D2-type dopamine receptors couple to $G\alpha_{i/o}$ proteins that inhibit adenylyl cyclase and cAMP production, resulting

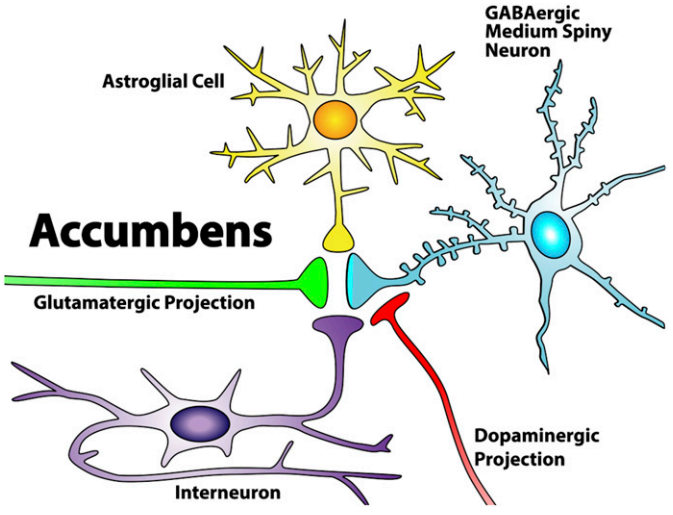

Fig. 2. NAc: the usual suspects. A general schematic of the some of the cell types discussed in this review that are present in the NAc, including MSNs (light blue), astrocytes (yellow), and various types of interneurons (purple). The accumbens receives inputs from several brain regions; examples of neurons that synapse in the accumbens are glutamatergic projection neurons (green) as well as dopaminergic projection neurons (red) (for more detail see Fig. 2).

in directly opposing effects on intracellular signaling and gene expression (Beaulieu and Gainetdinov, 2011). It has long been appreciated that these two populations display unique biochemical properties based on differences in dopaminergic signaling and gene expression profiles. The development of D1- and D2-fluorescent coupled bacterial artificial chromosome (BAC) transgenic mice, along with other technical advancements, allows investigators to more thoroughly explore the differences between D1- and D2-expressing MSNs both at a basic level and in disease models (Matamales et al., 2009; Valjent et al., 2009).

Regarding MSNs and drug-related behaviors, using BAC reporter strains reveals that both populations of cells make differential contributions to drug-associated behaviors, and drug-induced alterations in structure and function vary in the two subpopulations (Gong et al., 2003). Noncontingent cocaine injections induce phosphorylation of protein kinase A (PKA), extracellular signal–regulated kinase (ERK), and histone H3 specifically in D1 MSNs, whereas they reduce phospho-PKA and phospho-ERK in D2 MSNs (Bertran-Gonzalez et al., 2008; Goto et al., 2015). A recent comprehensive study examined the induction of ΔFosB in response to cocaine, ethanol, THC, and μ-opiates in D1 and D2 MSNs throughout the striatum and described drug-specific patterns of induction (Lobo et al., 2013). For example, cocaine, ethanol, and THC induced ΔFosB expression only in D1 MSNs in the NAcore, NAshell, and dorsal striatum, whereas morphine and heroin significantly induced ΔFosB in both cell types. Interestingly, similar patterns were observed between experimenter-administered and self-administered drug exposure (Lobo et al., 2013). To determine the behavioral consequences of cell type–specific induction of ΔFosB in the NAc, viral-mediated gene transfer was used to overexpress ΔFosB in D1 or D2 MSNs (Grueter et al., 2013). It was found that overexpression in D1 MSNs enhanced cocaine sensitization and CPP, whereas overexpression in D2 MSNs had no measured behavioral consequences (Grueter et al., 2013).

In addition to BAC transgenic mice, D1- and D2-Cre mice have been used to selectively express a number of exogenous proteins specifically in either MSN population and to create cell type–specific knockout animals. Using this strategy to selectively delete the brain-derived neurotrophic factor TrkB receptor in D1 or D2 MSNs, Lobo et al. (2010) demonstrated opposing effects on cocaine reward when measured by an unbiased CPP procedure, with the loss in D1 cells promoting and the loss in D2 cells reducing preference scores. Direct optogenetic activation of D1 or D2 MSNs similarly modulated cocaine reward in opposing directions (Lobo et al., 2010).

Overall, the emerging literature using these D1 and D2 transgenic mice supports a role for D1 MSNs in positively regulating psychostimulant-induced behavioral and cellular responses and D2 MSNs in negatively regulating these behaviors (Bertran-Gonzalez et al., 2008; Hikida et al., 2010; Lobo et al., 2010; Ferguson et al., 2011; Bock et al., 2013; Farrell et al., 2013; Park et al., 2013). Although the literature has been consistent in this regard, an important caveat that is discussed in more detail in this section is that although behaviors coded by D1 and D2 MSNs are traditionally interpreted as mediated by the direct and indirect pathways, respectively, D1 and D2 accumbens MSNs send a mixed projection to the VP, making the classic interpretation of direct and indirect pathways at least partly incorrect (Kupchik et al., 2015).

B. Interneurons

The 5%–10% of cells in the accumbens that are not MSNs are broadly classified as interneurons, and they can be chemically coded into several classes by their protein expression profile (Fig. 2) (Kawaguchi et al., 1995). Three discrete types of GABAergic interneurons are in the striatum: those that express parvalbumin; those that coexpress somatastatin, neuropeptide Y, and neuronal nitric oxide synthase (nNOS); and those that express calretinin (Tepper et al., 2010). Although parvalbumin- and calretinin-containing interneurons have been anatomically identified, their role in the physiology of drug addiction remains to be clearly elucidated and they are not discussed further. The fourth class of interneurons is cholinergic and is characterized by expression of choline acetyltransferase and relatively large soma.

1. Acetylcholine Interneurons. Cholinergic interneurons, which are also called giant aspiny neurons, are the most well studied interneuron population in the accumbens. Like other populations of interneurons, but in contrast with MSNs, these neurons are tonically active and are the primary source of acetylcholine (ACh) in the striatum (Calabresi et al., 2000). In addition to locally produced ACh, the accumbens receives cholinergic inputs from the brainstem, including the pedunculopontine and laterodorsal tegmental nuclei (Dautan et al., 2014) (see section III for details). Cholinergic interneurons are activated by cocaine self-administration, and blocking cholinergic receptors blocks cocaine reinforcement (Berlanga et al., 2003; Crespo et al., 2006). Although these neurons are responsive to both rewarding and aversive environmental stimuli, they differ from dopaminergic neurons in that they are maximally responsive to stimulus detection and context recognition (Aosaki et al., 1994; Apicella et al., 1997; Kimura et al., 2003), underscoring their potential importance for cue-induced reinstatement of drug seeking (see section II for a discussion of animal models of addiction). Optogenetic activation of ACh interneurons in the accumbens causes $GABA_A$-mediated inhibitory postsynaptic currents in MSNs in vivo, whereas optogenetically silencing these neurons causes an increase in MSN firing rate. Furthermore, silencing accumbens ACh neurons decreased

cocaine CPP, whereas activating these cells was not sufficient to drive or potentiate a place preference (Witten et al., 2010). Additional optogentic studies have shown that the inputs from the VTA to the ACh interneurons in the accumbens are selectively GABAergic, and activating GABAergic inputs (and thereby inhibiting ACh interneuron firing) enhanced outcome learning only to aversive stimuli (Brown et al., 2012).

ACh in the accumbens stimulates both the ionotropic nicotinic acetylcholine receptors (nAChRs) and the metabotropic muscarinic acetylcholine receptors (mAChRs). nAChRs are pentameric receptors that contain a combination of 12 possible subunits: $\alpha_{2\_}\alpha_{10}$ and $\beta_{2\_}\beta_4$. Binding of ACh to nAChRs allows cation flux that depolarizes neurons. mAChRs can be divided into two families: M1-like receptors (M1, M3, and M5) are Gq coupled and stimulate phospholipase signaling, whereas M2-like receptors (M2 and M4) are Gi coupled and inhibit adenylate cyclase. The primary muscarinic subtypes in the striatum are M1 and M4 (Sofuoglu and Mooney, 2009). Presynaptic M4 receptors on corticostriatal terminals negatively regulate glutamate release into the accumbens (Pancani et al., 2014), and muscarinic receptor activation also reduces inhibitory currents in MSNs, although it is not clear whether this is attributable to a presynaptic or postsynaptic effect (de Rover et al., 2002). Nicotinic receptor activation has no effect on accumbens MSN spontaneous excitatory postsynaptic currents (sEPSCs), but it significantly increased frequency and amplitude of $GABA_A$-mediated spontaneous inhibitory postsynaptic currents. This was action potential dependent and was blocked by 1 μM mecamylamine, which targets non–α7-containing nAChRs. On the basis of these observations, nAChRs likely contribute to action potential generation more than directly stimulating Ca^{2+}-dependent neurotransmitter release (de Rover et al., 2002).

Appetitive rewards increase ACh release in the accumbens, which was first demonstrated by studies showing that food- or water-deprived rats display ACh efflux immediately after food or water intake (Mark et al., 1992). Furthermore, antagonizing mAChRs via scopolamine significantly reduced lever pressing during sucrose self-administration, whereas the nAChR antagonist mecamylamine did not (Pratt and Kelley, 2005). Both D1-like and D2-like receptors can be found on the soma and dendrites of ACh interneurons (Alcantara et al., 2003); application of the D1 agonist SKF 82958 (3-allyl-6-chloro-1-phenyl-1,2,4,5-tetrahydro-3-benzazepine-7,8-diol) increases ACh efflux in the accumbens, whereas application of the D2 agonist quinpirole decreases ACh release (Consolo et al., 1999). However, it has been shown that physiologic dopaminergic input from the VTA slows cholinergic tonic activity, and a positron emission tomography study in baboons revealed that quinpirole, but not SKF 82958, increased binding of selective AChR radioligand norchloro[^{18}F]fluoroepibatidine (Ding et al., 2000). Cumulatively, these data indicate that cholinergic interneuron physiology is predominantly modulated by D2, rather than D1, receptors. However, noncontingent cocaine injections increase ACh in the dorsal and ventral striatum, and this effect can be blocked by D1 antagonist SCH 23390 (7-chloro-3-methyl-1-phenyl-1,2,4,5-tetrahydro-3-benzazepin-8-ol), supporting a role for D1 receptors in cocaine-induced neuroadaptations within the cholinergic system (Imperato et al., 1993; Consolo et al., 1999; Mark et al., 1999).

2. Somatostatin–, Neuropeptide Y–, and Neuronal Nitric Oxide Synthase–Expressing Interneurons. GABAergic interneurons that also express nNOS, somatostatin, and neuropeptide Y are a second class of interneurons in the accumbens (Kawaguchi et al., 1995). These cells constitute less than 1% of the accumbens neurons but have important consequences in mediating excitatory neurotransmission. nNOS enzymatically synthesizes the gaseous transmitter nitric oxide (NO) and is physically coupled to GluN2B-containing NMDARs via a PDZ interaction with postsynaptic density protein (PSD)-95, with Ca^{2+} influx through these receptors stimulating NO production (Christopherson et al., 1999). Specifically, nNOS is activated by calmodulin binding and synthesizes NO from L-arginine (Hayashi et al., 1999). NO can diffuse directly through lipid bilayers to affect extracellular, presynaptic, and postsynaptic targets. Canonical NO signaling is through binding to soluble guanylate cyclase (sGC), whereby sGC activation increases cGMP formation to stimulate protein kinase G and affect ERK phosphorylation and CREB-mediated changes in gene expression (Gabach et al., 2013). Although sGC is the only known receptor for NO, the reactive nitrogen chemical properties of NO allow it to *S*-nitrosylate a great number of proteins, and this post-translational modification is involved in modifying the activity state and/or binding properties of many enzymes and proteins (Jaffrey et al., 2001; Gu et al., 2002; Selvakumar et al., 2009).

After 7 days of experimenter-administered cocaine injections and 14 days of withdrawal, NO efflux is increased in the dorsal striatum (Lee et al., 2010), yet nitrergic signaling in the NAc is relatively understudied. However, a recent important study demonstrates that in the NAshell, *S*-nitrosylation of the AMPA trafficking protein Stargazin is required for the increased surface expression of GluA1 AMPARs underlying behavioral sensitization to cocaine, supporting involvement of NO in the accumbens in the effects of addictive drugs (Selvakumar et al., 2014). In addition, GluA1 subunits can be *S*-nitrosylated directly, which increases channel conductance (Selvakumar et al., 2013). Furthermore, the extracellular endopeptidases matrix metalloproteinase (MMP)-2 and MMP-9 are activated by *S*-nitrosylation (Gu et al., 2002); in the accumbens core, these enzymes are required for synaptic plasticity

mediating cue-induced reinstatement of cocaine, heroin, and nicotine seeking (Smith et al., 2014).

C. Glial Cells

Astrocytes regulate glutamatergic synaptic plasticity within the accumbens by controlling the extracellular glutamate concentration via coordinated uptake and release (Kalivas, 2009). Glial cells release glutamate in a variety of ways (Scofield and Kalivas, 2014), including through the cystine-glutamate exchanger (system x_c-) (Malarkey and Parpura, 2008). System x_c- catalyzes the 1:1 release of astrocytic glutamate in exchange for extracellular cystine, a mechanism that provides more than 50% of the extrasynaptic glutamate measured in the NAcore via in vivo microdialysis (Hascup et al., 2008; van der Zeyden et al., 2008). Interestingly, chronic cocaine and nicotine exposure downregulate expression of x_c- (Moran et al., 2003; Kalivas, 2009; Knackstedt et al., 2009), which serves as a plausible mechanistic explanation for the decrease in basal glutamate levels observed after chronic exposure to these drugs (Table 1). The maintenance of extracellular glutamate levels through system x_c- is of central importance in the regulation of synaptic plasticity in the corticoaccumbens circuit because it provides tone on presynaptic mGluR2/3 autoreceptors that regulate the synaptic release of glutamate (Moran et al., 2005). As such, drug-induced reduction of glutamate tone onto mGluR2/3 promotes synaptic potentiation and enhances glutamate release induced by conditioned cues and drug exposure. This potentiated release causes synaptic glutamate spillover and access of extracellular glutamate to postsynaptic glutamate receptors, which engages synaptic plasticity responsible for drug-seeking behavior (Kalivas, 2009).

After neuronal synaptic glutamate release, astrocytes terminate signaling by removing glutamate from the synaptic cleft through the patterned expression of the Na^+-dependent glial glutamate transporter (GLT)-1 (EAAT2) (Williams et al., 2005). This glial function is required for the fidelity of glutamatergic synaptic communication and protection from excitotoxicity, since GLT-1 is responsible for more than 90% of uptake in the brain (Danbolt, 2001). Chronic exposure to several classes of addictive substances, including cocaine, nicotine, ethanol, and heroin, reduces expression of GLT-1 (Knackstedt et al., 2010a; Sari and Sreemantula, 2012; Gipson et al., 2013b; Shen et al., 2014b; Reissner et al., 2015). As such, GLT-1 downregulation may serve as a common drug-induced neuroadaptation contributing to relapse vulnerability. Mechanistically, lack of glutamate uptake in the NAc promotes spillover of synaptically released glutamate out of the synaptic cleft and into the extracellular space, causing the activation of postsynaptic glutamate receptors responsible for the rapid transient synaptic potentiation associated with relapse (see the detailed discussion in section V).

TABLE 1
Glutamate dynamics

Downward arrows indicate a decrease, upward arrows indicate an increase, and question marks indicate that this experimental outcome has not yet been tested.

Drug	GLT-1 Expression/ Function	Restoration of GLT-1 Decreases Reinstatement	xCT Expression/ Function	Basal NACore Extrasynaptic Glutamate	Glutamate Release During Drug Seeking	Effects of Agonism of mGluR2/3 on Reinstatement	Effects of Antagonism of mGluR5 on Reinstatement	Effects of Astroglial Gq-DREADD Activation on Reinstatement
Cocaine	↓ (Knackstedt et al., 2010a; Trantham-Davidson et al., 2012; Reissner et al., 2015)	(Knackstedt et al., 2010a; Moussawi et al., 2011; Sondheimer and Knackstedt, 2011; Reissner et al., 2015)	↓ (Baker et al., 2003; Knackstedt et al., 2010a)	↓ (Baker et al., 2003)	↑ (McFarland et al., 2003)	↓ (Peters and Kalivas, 2006; Cannella et al., 2013)	↓ (Kumaresan et al., 2009; Knackstedt et al., 2014; Wang et al., 2013)	↓ (Scofield et al., 2015)
Nicotine	↓ (Knackstedt et al., 2009; Gipson et al., 2013b)	(Alajaji et al., 2013; Ramirez-Niño et al., 2013)	↓ (Knackstedt et al., 2009)	Unchanged (Gipson et al., 2013b)	↑ (Gipson et al., 2013b)	↓ (Liechti et al., 2007)	↓ (Bespalov et al., 2005; Dravolina et al., 2007)	Untested
Opiates	↓ (Shen and Kalivas, 2013)	(Zhou and Kalivas, 2008)	↑ (Shen and Kalivas, 2013)	??	↑ (LaLumiere and Kalivas, 2008)	↓ (Bossert et al., 2005, 2006)	↓ (Popik and Wróbel, 2002; Brown et al., 2012)	Untested
Ethanol	↓ (Melendez et al., 2005; Sari et al., 2013) or unchanged (Griffin et al., 2014)	Untested	Unchanged sodium-independent uptake (Griffin et al., 2014)	↑ (Griffin et al., 2014)	↑ (Gass et al., 2011)	↓ (Zhao et al., 2006; Griffin et al., 2014)	↓ (Bäckström and Hyytiä, 2004; Sinclair et al., 2012)	↓ (Bull et al., 2014)
Methamphetamine	Untested	Untested	Untested	↓ (Parsegian and See, 2014); ↑ (Lominac et al., 2012)	↑ (Parsegian and See, 2014)	↓ (Kufahl et al., 2013)	↓ (Gass et al., 2009; Watterson et al., 2013)	Untested

xCT, the catalytic subunit of the cystine-glutamate exchanger.

D. Extracellular Matrix

A proteinacous network of secreted macromolecules deemed the extracellular matrix (ECM) supports the complex architecture of interconnected neural and glial processes in the neuropil. The ECM comprises approximately 20% of the volume of the mature brain (Nicholson and Syková, 1998) and has a highly organized composition consisting of two main classes of proteins: glycosaminoglycans normally linked to proteins in the form of proteoglycans and fibrous proteins including laminin, collagen, elastin, and fibronectin. The ECM not only serves as a structural anchor for neurons and glia, but it is also a signaling domain that regulates neurotransmission, cellular growth, plasticity, and apoptosis/survival signaling (Lee et al., 2001; Gu et al., 2002; Verslegers et al., 2013). Furthermore, signaling between neurons and the ECM is bidirectionally transduced; that is, changes in the extracellular milieu can affect intracellular signaling (outside-in signaling), and changes in the intracellular environment can be transduced to signaling within the ECM (inside-out signaling).

All parts of the tripartite synapse (presynapse, postsynapse, and glia) interact either directly or indirectly with the ECM (Dityatev and Rusakov, 2011). One such method for interaction is through cell adhesion molecules (CAMs), which are transmembrane proteins that bind to ECM glycoproteins and also to intracellular signaling molecules to organize the synaptic interface and regulate synaptic activity (Shinoe and Goda, 2015). The integrins and the intracellular CAMs are the most well studied CAMs in the brain (Wiggins et al., 2011; Niedringhaus et al., 2012; Lonskaya et al., 2013). Because the ECM can respond to activity in the other three compartments of the tripartite synapse, it is now considered a fourth synaptic compartment, causing the emergence of the term *tetrapartite synapse* (for review, see Smith et al., 2015a). For example, activity-dependent ECM signaling can liberate latent growth factors (Saygili et al., 2011), affect synaptic and extrasynaptic receptor content (Michaluk et al., 2009), and stimulate morphologic and physiologic synaptic plasticity (Wang et al., 2008).

The ECM must be degraded to allow morphologic plasticity of dendritic spines (discussed in greater detail in section V), making catabolic enzymes essential for the induction of classic forms of synaptic plasticity, such as LTP (Wang et al., 2008; Szepesi et al., 2013). MMPs are the family of zinc-dependent endopeptidases that degrade ECM proteins and are permissive to a number of events classically associated with synaptic plasticity, including morphologic changes in dendritic spines (Michaluk et al., 2011; Stawarski et al., 2014; Verslegers et al., 2015), NMDAR lateral diffusion, and AMPAR phosphorylation and insertion (Michaluk et al., 2009; Szepesi et al., 2014). Specifically, MMP-2 and MMP-9 play important roles in aberrant synaptic plasticity associated with neurologic disorders (Mizoguchi et al., 2011; Stawarski et al., 2014), with recent research demonstrating the importance of MMPs in drug behavioral effects and relapse. For example, inhibiting MMP-9 attenuates cocaine CPP (Brown et al., 2008), and MMP-9 is involved in regulating synaptic plasticity underlying acquisition of nicotine CPP (Natarajan et al., 2013). In addition, MMP-9 activation is implicated in the development of morphine tolerance (Nakamoto et al., 2012). MMP activity in the hippocampus (namely, MMP-9 activity) is disrupted after ethanol exposure and thereby impairs acquisition of a spatial memory task (Wright et al., 2003). Interestingly, MMP activity is associated with the transient plasticity found during cue-induced cocaine reinstatement (Smith et al., 2014). Specifically, MMP-2 activity in the NAcore is constitutively elevated after extinction of cocaine self-administration, and inhibiting this activity reversed cocaine-induced potentiation of the spine head diameter and the AMPA/NMDA ratio. Furthermore, MMP-9 activity is transiently increased during cue-induced cocaine reinstatement, and blockade of this induction also blocks the transient synaptic potentiation, which accompanies reinstatement (Smith et al., 2014). In addition, cue-induced heroin and nicotine seeking increases MMP-2/MMP-9 activity, and MMP activity is also required for synaptic plasticity underlying escalation of ethanol intake after chronic exposure (Smith et al., 2011).

MMP-2 and MMP-9 are unique within the metalloproteinase superfamily for their ability to recognize and expose arginine-glycine-aspartate domains that are endogenous ligands at the integrin family of CAMs (Verslegers et al., 2013). Application of recombinant, autoactive MMP-9 to hippocampal slices drives LTP of field potentials and spine head enlargement even in the absence of high-frequency stimulation, and this effect is occluded by a β1-integrin blocking antibody (Wang et al., 2008). Integrins are coupled to the integrin-linked kinase, which can phosphorylate GluA1 at Serine 845, driving the Ca^{2+}-permeable (CP) AMPARs into the synapse (Chen et al., 2010). Integrin-linked kinase can also phosphorylate cofilin to stimulate actin polymerization and dendritic spine enlargement (Kim et al., 2008). The β3-integrin subunit is increased in the PSD subfractionation of rats that have undergone 21 days of extinction of cocaine self-administration, whereas expression of the β1-subunit remains unchanged (Wiggins et al., 2011). The β3 subunit is physically coupled to AMPARs via their cytoplasmic domains (Pozo et al., 2012) and is required for activity-dependent synaptic scaling of glutamatergic synapses (Cingolani et al., 2008). For more information on the ECM, MMPs, and tissue inhibitors of MMPs, see Seals and Courtneidge (2003), Brew and Nagase (2010), Huntley (2012), Oohashi et al. (2015), Singh et al.

(2015), Smith et al. (2015a,b), and Vafadari et al., (2015).

IV. Nucleus Accumbens: Connectivity

The NAc was first described in the early 1900s by Theodor Ziehen as the "nucleus accumbens septi" (area leaning against the septum), owing to its location near the midline and its assumed role as part of the septal or olfactory system. In the 1970s, histochemical and tracing methods changed this view (Heimer et al., 1997) and the accumbens is now considered to be an integral part of the striatum, with which it is contiguous and with which it has common neuronal composition and the expression of histochemical markers (see section II above for details on accumbens neuronal subtypes). Generally speaking, the accumbens has a similar basic connectivity pattern as the dorsal striatum, in that it receives dense dopaminergic input from the ventral mesencephalon and glutamatergic input from cortical, allocortical, and thalamic brain regions and sends GABAergic projections that do not leave the basal ganglia. The overall topography of cortical and allocortical input makes the NAc the principal striatal portal for limbic and appetitive input, and it is critically positioned to regulate motivated behavior (Mogenson et al., 1980; Alexander et al., 1990; Heimer et al., 1997; Groenewegen et al., 1999; Haber, 2003).

Selective histochemical tracing and immunostaining techniques allowed for the dissection of inputs to the NAc and revealed a subdivision of the structure into a central core region and surrounding shell (Voorn et al., 1989). The core appears to be a canonical basal ganglia structure, in that its projections remain within the basal ganglia. However, the shell projects to regions outside of the basal ganglia, such as the hypothalamus and parts of the extended amygdala, perhaps fitting the original designation of the accumbens as part of the septum (Heimer et al., 1997; Groenewegen et al., 1999).

To assess contributions of specific accumbens projections to drug-related behaviors, pharmacological disconnection studies have long been a gold standard (McFarland and Kalivas, 2001; Di Ciano and Everitt, 2004). In these studies, it is assumed that similar unilateral serial circuits exist in both hemispheres of the brain and, as such, inactivating two different serially connected nuclei in a contralateral fashion can reveal insight about a projection. However, since axonal terminals are not directly manipulated using this technique and some projections to the accumbens are bilateral, a direct projection can never be assumed with this particular type of study. Other traditional techniques to assess addiction circuits involve the electrical stimulation of one brain region and electrophysiological recording in another (Moussawi et al., 2009), or the pharmacological inactivation of one brain region combined with microdialysis sampling of the major neurotransmitter in this projection in the downstream area (McFarland et al., 2003; LaLumiere and Kalivas, 2008). In addition, tracer injections combined with neuronal activity markers [immediately early gene (IEG) products] are sometimes used to define neuronal activity–dependent projections related to behavioral effects of drugs (Marchant et al., 2009; Mahler and Aston-Jones, 2012).

These techniques are now complemented with more selective opto- and chemogenetic approaches that allow for precise temporal, cell type–specific, and pathway-specific disconnection of neuronal projections in freely behaving animals (Boyden et al., 2005; Sternson and Roth, 2014). Within the addiction literature, these techniques are becoming the standard for NAc circuit manipulations (Stefanik et al., 2013b; Mahler et al., 2014b; Larson et al., 2015; Kerstetter et al., 2016). Another recent advance in genetic circuit deconstruction incorporates the tagging of neuronal ensembles during a specific behavior for later manipulations. By employing IEG activity in response to neuronal activity, these and similar genetic approaches are used to investigate the role of drug-associated ensembles of neurons (memory traces or engrams) associated with these behaviors (Hsiang et al., 2014; Cruz et al., 2015; Tonegawa et al., 2015; see section VIII.B for more information on cocaine-associated engrams).

Below we discuss the basic anatomy of afferents (inputs) and efferents (outputs) of the NAc and present findings to elucidate the role of each projection where information is available on the specific role of that projection in addiction circuitry. We also briefly discuss the effects of NAcore versus shell NAshell inactivation manipulations on drug-related behavior, with a selective focus on the drug self-administration model. For an in-depth description of drug-induced electrophysiological changes in specific projections, see section V.

Inputs from most brain regions to the NAc are organized along a topographic gradient. For instance, hippocampal inputs are organized along the dorsoventral (septotemporal) axis such that dorsal structures preferably target the NAcore and ventral structures target the NAshell (Voorn et al., 2004; Strange et al., 2014). Similar organization exists along the dorsoventral axis of the medial prefrontal and cingulate cortex and anteroposterior axis of the BLA and paraventricular thalamus, which project to the core and shell subcompartments of the accumbens, respectively (Groenewegen et al., 1999; Voorn et al., 2004) (Fig. 1). This organization suggests that parallel information streams from these regions may be important for distinct striatal processes (Voorn et al., 2004) (e.g., distinct limbic and motor processes; Kalivas, 2009).

A. Nucleus Accumbens Core

The NAcore is responsible for the evaluation of reward and initializing reward-related motor action

(Voorn et al., 2004; Sesack and Grace, 2010; Shiflett and Balleine, 2011). It serves as an intermediate between the NAshell responsible for reward prediction and reward learning and the dorsolateral striatal regions responsible for the encoding and execution of learned habits, skills, and action sequences (Shiflett and Balleine, 2011). The NAcore is essential for acquiring drug-taking behaviors and cue-elicited drug-seeking responses. For psychostimulant drugs, learning drug reward associations is largely dependent on dopaminergic and glutamatergic signaling within the NAcore, whereas reinstatement is mostly driven by glutamate (Kalivas and Volkow, 2005; Koob and Volkow, 2010). However, it is important to note that additional neurochemical mechanisms are involved in drug reward associations and reinstatement of nonpsychostimulant drugs such as opiates and benzodiazepines (for review, see Badiani et al., 2011; Nutt et al., 2015).

1. Glutamatergic Afferents. The NAcore receives glutamatergic inputs from several cortical areas. Both the dorsomedial PFC (prelimbic and anterior cingulate) and the dorsolateral PFC (anterior insular) innervate the NAcore and are likely to send associative motivationally relevant information (Sesack et al., 1989; Brog et al., 1993). The NAcore further receives spatial and declarative information from the parahippocampal formation through the perirhinal and entorhinal cortex (Brog et al., 1993).

With regard to drug-related behaviors, glutamate originating from the PLC is necessary for the reinstatement of drug seeking (McFarland et al., 2003). Furthermore, disconnection of the PLC and VP with a GABAergic agonist cocktail (baclofen plus muscimol) prevents cocaine-primed reinstatement of drug seeking, suggesting that a serial circuit from the PLC to the NAcore to the VP is responsible for drug seeking (McFarland and Kalivas, 2001). Indeed, using an optogenetic strategy, selectively inhibiting PLC-to-NAcore or NAcore-to-VP projections abolishes cocaine-primed drug seeking (Stefanik et al., 2013a,b).

In addition to driving cocaine-primed reinstatement, projections from the dorsomedial PFC to the accumbens drive stress-induced and cue-induced reinstatement of cocaine seeking (McFarland and Kalivas, 2001; McFarland et al., 2003, 2004; Gipson et al., 2013a; Stefanik et al., 2013b; Kerstetter et al., 2016). In line with the idea that projections from the PLC to the NAcore drive various forms of relapse behavior to cocaine, a recent study also investigated the effect of manipulating this pathway on the incubation of cocaine craving after long-term abstinence (see section II for details of this animal model). Selective depotentiation of PLC-to-NAcore projection using optogenetics reduced the incubation of cocaine seeking (Ma et al., 2014). Glutamate originating from the PLC was also shown to be necessary for cue-induced reinstatement of nicotine seeking and heroin seeking (LaLumiere and Kalivas, 2008; Gipson et al., 2013b). In addition, although direct projections have not yet been tested, both the PLC and NAcore are necessary for the cue-induced reinstatement of heroin, methamphetamine, ethanol, and 3,4-methylenedioxymethamphetamine seeking (Rogers et al., 2008; Chaudhri et al., 2010; Rocha and Kalivas, 2010; Ball and Slane, 2012; Willcocks and McNally, 2013). Combined, these studies point to the PLC to NAcore as a final common pathway for cue-elicited relapse to drug seeking (Kalivas, 2009).

More recent studies investigated the involvement of PFC-to-NAcore projection in other drug-related behaviors. Inhibiting projections from the anterior cingulate to the NAcore increases motivation to obtain cocaine under a PR schedule of reinforcement, delays subsequent extinction, and increases reinstatement (Kerstetter et al., 2016). This is in line with other work suggesting a differential role of the PLC-to-NAcore circuitry during different stages of the addiction process (Chen et al., 2013; Martín-García et al., 2014).

Apart from cortical inputs, several allocortical projections from nuclei in the BLA terminate into the NAcore (Kelley et al., 1982; McDonald, 1991; Brog et al., 1993) and pharmacological disconnection of this pathway inhibits cocaine self-administration (Di Ciano and Everitt, 2004). Projection from the BLA to NAcore is also necessary for drug seeking, because either pharmacological or optogenetic inhibition of the projection blunts cue-induced reinstatement of cocaine seeking (See, 2002; Stefanik and Kalivas, 2013). Furthermore, the BLA-to-NAcore pathway is also involved in natural reinforcement, because optical stimulation of amygdala-accumbens fibers stimulates responding for sucrose (Stuber et al., 2011). Finally, the NAcore receives glutamate from various other sources, including the paraventricular and intralaminar nuclei of the thalamus (Vertes and Hoover, 2008) and hippocampal formation (Kelley et al., 1982; Groenewegen et al., 1987; Brog et al., 1993).

2. γ-Aminobutyric Acidergic Afferents. Both NAcore and NAshell subregions receive reciprocal connections from the VP. Recent data from our laboratory demonstrate that the GABAergic projection from the VP to the NAcore is not involved in the reinstatement of cocaine seeking (Stefanik et al., 2013a). Another major source of GABA to the NAcore originates from the VTA (Taylor et al., 2014). Although this projection has not been studied extensively in the context of addiction, recent work shows that VTA GABA-mediated inhibition of NAc cholinergic interneurons facilitates associative learning processes (Brown et al., 2012), suggesting that these GABA afferents may play an important role in drug memories and related plasticity. Finally, the NAcore receives GABAergic inputs from the lateral septum (Brog et al., 1993) and a minor GABAergic input from medial prefrontal parvalbumin projection neurons (Lee et al., 2014), but these have yet to be investigated in drug-related behaviors.

3. Dopaminergic Afferents. The NAcore receives dopaminergic input from the substantia nigra pars compacta and VTA. VTA inputs to the NAcore are necessary for reinstatement of cocaine seeking and associated changes in structural plasticity (Stefanik et al., 2013a; Shen et al., 2014a). Interestingly, infusions of AMPAR antagonists in the NAcore inhibit cocaine-primed reinstatement, whereas application of dopamine antagonists is ineffective (Cornish and Kalivas, 2000; McFarland and Kalivas, 2001). Conversely, either D1 or D2 receptor inhibition in the NAshell prevents cocaine-primed reinstatement, yet these drugs have no effect in the NAcore (Anderson et al., 2003, 2006). Taken together, these studies show that NAcore glutamate, and not dopamine signaling, drives drug seeking. Furthermore, they pose the possibility that glutamate in the VTA-to-NAcore projection may be responsible for the effects of VTA inhibition on reinstatement behavior and plasticity (Stuber et al., 2010).

4. Nucleus Accumbens Core Efferents. The NAcore sends projections primarily to GABAergic basal ganglia nuclei, but it also contains neurons that send inputs directly to glutamatergic neurons in the subthalamus and dopaminergic neurons in the paranigral part of the VTA (Groenewegen et al., 1999; Tripathi et al., 2010; Watabe-Uchida et al., 2012; Bocklisch et al., 2013; Matsui et al., 2014; Kupchik et al., 2015). The NAcore also projects to the substantia nigra pars reticulata and sends a striatopallidal projection to the dorsolateral VP and lateral globus pallidus (Heimer et al., 1991; Tripathi et al., 2010). With regard to addiction circuitry, recent optogenetic data from our laboratory show that the pallidal, but not the nigral, projection drives cocaine seeking (Stefanik et al., 2013a). This observation extends the previous finding that a serial circuit between the PLC, NAcore, and VP is necessary for reinstatement, whereas the substantia nigra is not involved in this behavior (McFarland and Kalivas, 2001). Involvement in the striatopallidal projection from the core has also recently been demonstrated for alcohol seeking (Perry and McNally, 2013). Furthermore, projections from the NAcore to the VTA were shown to have significantly elevated levels of Fos after cue-induced reinstatement of cocaine seeking, suggesting that despite the apparent lack of involvement shown with inactivation strategies, a direct projection from the NAcore to the VTA may be involved in the motivation to seek drugs (Mahler and Aston-Jones, 2012).

Most MSNs in the accumbens discretely express either D1 or D2 mRNA and are considered different populations with opposing roles in the addiction circuit (Smith et al., 2013). The D1 and D2 cell types have traditionally been distinguished on the basis of unique projection profiles in the dorsal striatum. D1-expressing MSNs send axon terminals to output structures of the basal ganglia (e.g., globus pallidus and substantia nigra) and are classified as belonging to the "direct" pathway. Conversely, D2-expressing neurons terminate in intrinsic basal ganglia structures (endopeduncular nucleus and subthalamic nucleus) and contribute to the "indirect" pathway because these output structures do not project directly out of the basal ganglia to the thalamus (Gerfen and Surmeier, 2011). This categorization originated from observations in the dorsal striatum, wherein D1 and D2 axons do indeed traverse along independent direct and indirect pathways. Moreover, the segregation has been useful to explain the physiology of the basal ganglia in regulating motor movements, because corticostriatal activation of the direct D1 pathway results in disinhibition of thalamocortical output and the facilitation of movement, whereas activation of the indirect D2 pathway suppresses movement (Kravitz et al., 2010). Although recent research has highlighted a small fraction of D1-MSN collaterals projecting to the globus pallidus externus alongside D2-MSN inputs, the preponderance of MSN efferents from the dorsal striatum (caudate and putamen in humans) remains segregated into the direct and indirect pathways according to D1 versus D2 expression, respectively (Nadjar et al., 2006; Matamales et al., 2009; Saunders et al., 2015). However, this assumption does not hold true for the accumbens efferents in which substantial involvement of D1 MSNs in the indirect projections and D2 MSNs in the direct projections can be demonstrated. Projections from these cells to the VP are a mixture of D1 and D2 MSN axons (Lu et al., 1998; Zhou et al., 2003; Smith et al., 2013; Kupchik et al., 2015). Selective optogenetic stimulation of D1- or D2-MSN projections to the VP revealed that virtually all VP neurons respond to optically evoked D2 inputs from the NAcore, and about one-half the cells respond to D1 stimulation (Kupchik et al., 2015).

The VP can be considered both an intrinsic (indirect) and an output (direct) structure of the basal ganglia, owing to its anatomic connectivity with the subthalamic nucleus and ventral mesencephalon on one hand (indirect pathway) and the presence of direct projections out of the basal ganglia to the mediodorsal thalamus on the other (Zahm, 1989; Zahm and Heimer, 1990; Kalivas et al., 1993; Churchill et al., 1996; Maurice et al., 1997). This raises the possibility that D1 and D2 projections from the accumbens to the VP might give rise to distinct direct and indirect pathways through the VP (Sesack and Grace, 2010; Smith et al., 2013; Tripathi et al., 2013). However, recent work using transgenic D1- and D2-Cre mouse lines demonstrates that unlike the dorsal striatum, D1 and D2 afferents to the VP do not distinguish between direct or indirect basal ganglia pathways (Kupchik et al., 2015). In contrast, the coding of direct projections from the accumbens to the ventral mesencephalon is identical to the direct projections from the dorsal striatum and is composed of only D1-expressing neurons (Watabe-Uchida et al., 2012; Bocklisch et al., 2013; Kupchik et al., 2015).

B. Nucleus Accumbens Shell

The NAshell is the primary striatal region involved with motivation and reward-related processes. Akin to nonstriatal basal ganglia nuclei, the shell is heavily interconnected with regions such as the lateral hypothalamus and extended amygdala and is therefore often considered a transition zone that serves as a point of convergence between these systems (Sesack and Grace, 2010). It is thus ideally positioned to process motivationally relevant information in accordance with autonomic, emotional, and basal ganglia systems (Heimer et al., 1997).

1. Glutamatergic Afferents. The medial portion of the NAshell receives glutamatergic projections from the ventromedial [infralimbic cortex (ILC), ventral PLC, medial orbitofrontal cortex, and dorsal peduncular cortex] and ventrolateral (anterior insular) PFC (Sesack et al., 1989; Brog et al., 1993; Heimer et al., 1997; Groenewegen et al., 1999; Ma et al., 2014). Recent studies have begun to elucidate the role of specific prefrontal inputs to the NAshell in addiction-related behaviors. Although neither the ILC or NAshell appears to be important for drug-seeking behavior guided by cues, it is crucial for drug-primed and context-induced reinstatement of cocaine seeking (McFarland and Kalivas, 2001; Anderson et al., 2003; Cruz et al., 2013). In addition, the ILC-to-NAshell pathway is necessary for context-induced heroin seeking (Bossert et al., 2007, 2012). This apparent contradiction to the role of the ILC-NAshell pathway in cocaine and heroin seeking may be reconciled as a difference in context- versus drug-primed reinstatement or as a difference in circuits recruited by these different drugs (Rogers et al., 2008; Peters et al., 2013). Moreover, work from our laboratory shows that glutamatergic input from the ILC is necessary for extinction learning after exposure to cocaine and that glutamatergic input is required for proper recall of extinction memory (Peters et al., 2008; LaLumiere et al., 2010). Interestingly, the suppression of cocaine seeking by the ILC-NAshell pathway can be overruled by direct injection of dopamine into the shell, showing that the NAshell can either drive or inhibit drug seeking depending on what information it receives (LaLumiere et al., 2012).

Glutamatergic synapses in the ILC-NAshell pathway are silenced after cocaine exposure and abstinence from cocaine unsilences these synapses through the insertion of calcium-permeable (GluA2-lacking) AMPARs into the membrane (see section V for further details) (Conrad et al., 2008; Ma et al., 2014). Similarly, both short and long withdrawal from contingent or noncontingent cocaine exposure enhances the release probability for glutamate from the ILC-NAshell pathway (Suska et al., 2013). These processes may offer a physiologic underpinning of behavioral inhibition after abstinence or extinction, because selectively reversing this synaptic mechanism or inhibiting the pathway results in relapse to cocaine seeking (Peters et al., 2008; Ma et al., 2014).

Repeated noncontingent administration of cocaine reduces the ability of synapses onto D1 MSNs, but not D2 MSNs, to undergo synaptic plasticity (LTP). This effect coincides with typical increases in locomotor sensitization, and reversal of this synaptic deficit by applying an optogenetic LTD protocol in vivo abolishes cocaine-induced sensitization (Pascoli et al., 2012). Similarly, abstinence from cocaine self-administration reduces synaptic strength in the ILC-NAshell pathway, and reversing this deficit using optical LTD reduces cue-induced drug seeking (Pascoli et al., 2014).

In addition to cortical input, the medial NAshell also receives allocortical inputs from parts of the BLA complex (McDonald, 1991). Repeated noncontingent cocaine exposure increases the strength of BLA inputs specifically to D1 MSNs in the medial NAshell (MacAskill et al., 2014). In line with this finding, withdrawal from cocaine self-administration leads to incubation and results in insertion of the GluA2-lacking AMPAR in the BLA-to-NAshell pathway (Lee et al., 2013). Optogenetic LTD-mediated reversal of GluA2-lacking AMPAR–mediated plasticity in this pathway reduces cocaine seeking (Lee et al., 2013). In addition, context-induced reinstatement of alcohol seeking recruits BLA neurons that project to the medial shell (Hamlin et al., 2009). These results point to the possibility that glutamate has pathway-specific effects that either drive (BLA-NAshell) or inhibit (ILC-NAshell) drug seeking after abstinence.

Akin to this idea for BLA-NAshell, inputs from the ventral hippocampus (vHPC) are also a major regulator of the reinforcing effects of cocaine. The medial shell receives allocortical glutamatergic inputs from the ventral subiculum and ventral CA1 region (vHPC) (Groenewegen et al., 1987; Brog et al., 1993; Strange et al., 2014). Retrograde tracing reveals a greater amount of NAshell-projecting neurons from the vHPC than the BLA or medial prefrontal cortex (mPFC) (Britt et al., 2012). Several studies show that repeated contingent or noncontingent cocaine potentiates vHPC-NAshell synapses (Britt et al., 2012; Pascoli et al., 2014). Furthermore, optical inhibition or excitation of vHPC inputs inhibited or facilitated cocaine-induced locomotor sensitization and preference for a laser-paired room in a real-time place preference test (Britt et al., 2012). The importance of inputs from the vHPC to the medial NAshell was further demonstrated by Pascoli et al. (2014), who showed that reversing cocaine-induced synaptic plasticity optogenetically reduces reinstatement of cocaine seeking.

The medial shell also receives input from the periventricular nucleus of the thalamus (PVT) (Brog et al., 1993). These projections terminate close to dopamine terminals, which suggests that these inputs may control

dopamine levels in the shell and thereby exert effects over addiction-related behaviors (Pinto et al., 2003). In line with this, recent studies suggest that the PVT is involved in mediating cue-induced reinstatement to cocaine seeking, and PVT neurons that project to the medial NAshell have significantly elevated levels of Fos immunoreactivity after context-induced reinstatement of alcohol seeking (Hamlin et al., 2009).

The ventral and lateral subcompartments of the NAshell receive selective glutamatergic input from the ventrolateral PFC, BLA, and posterior PVT (Brog et al., 1993; Groenewegen et al., 1999). Although the role of the lateral shell has been relatively less understood in addiction processes, a recent study shows that blocking the AMPAR in either the NAcore or medial or lateral NAshell similarly impairs context-induced reinstatement of cocaine seeking (Xie et al., 2012)

2. Dopaminergic Afferents. Dopaminergic inputs to the medial shell are mostly derived from the VTA (Beckstead et al., 1979). The role of dopamine in the NAshell has been well studied using pharmacological approaches. For instance, direct infusion of a D1 or D2 receptor antagonist in the shell blocks cocaine-primed reinstatement (Anderson et al., 2003, 2006). Conversely, D1 or D2 receptor activation in the shell triggers cocaine seeking in extinguished animals (Schmidt and Pierce, 2006). The lateral subcompartments of the NAshell receive dopaminergic input instead from the lateral VTA and retrorubral (A9) cell group (Beckstead et al., 1979). Both VTA neurons projecting to the lateral shell and medial shell undergo synaptic plasticity after noncontingent cocaine exposure, but only ventral midbrain dopamine cells projecting to the lateral shell show increased plasticity after punishment. This suggests that the lateral shell may drive general salience, regardless of positive or negative value (Lammel et al., 2012). A potential role of the lateral shell in cocaine-related behavior was demonstrated by increased IEG expression in ventrolateral NAshell neurons projecting to the VTA during reinstatement (Mahler and Aston-Jones, 2012). D1 antagonists in either the medial and lateral NAshell attenuate context-induced reinstatement of heroin seeking; this suggests that like glutamatergic signaling, the main role of dopamine is similar in the medial and lateral shell with regard to drug seeking (Bossert et al., 2007).

3. Other Afferents. In addition to monoaminergic inputs from the VTA, the NAshell receives noradrenaline from the locus coeruleus and nucleus of the solitary tract (Delfs et al., 1998). Although the role of noradrenaline in the NAshell in drug-seeking behavior has not been explored, noradrenaline increases dopamine release in this region through the $\alpha 1$ receptor and blocking this receptor specifically in the NAshell reduces cocaine-induced locomotor activity (Mitrano et al., 2012). Other brainstem inputs to both the NAcore and NAshell include the dorsal raphe, which sends serotonergic and nonserotonergic projections, and neurons in the pedunculopontine tegmentum and laterodorsal tegmentum (Brown and Molliver, 2000; Dautan et al., 2014). Although this projection has not been not explored in detail, pharmacological inactivation of the pedunculopontine tegmental nucleus reduces cocaine-primed reinstatement of drug seeking (Schmidt et al., 2009).

4. Efferents of the Nucleus Accumbens Shell. The medial NAshell projects to the ventromedial VP, which in turn projects to the medial part of the mediodorsal thalamus and VTA (Heimer et al., 1991; Tripathi et al., 2013). In addition, the medial NAshell projects to the lateral hypothalamus, a projection that may provide essential regulation of autonomous systems related to reward (Heimer et al., 1997). Indeed, recent studies show that neurons in the medial shell to the lateral hypothalamus pathway show elevated levels of the activity marker c-Fos during extinction of alcohol seeking (Marchant et al., 2009; Millan et al., 2010). On the other hand, projections from the ventral NAshell to the lateral hypothalamus mediate reinstatement of alcohol seeking (Marchant et al., 2009). This circuit was also activated by context-induced renewal of alcohol seeking after punishment-induced abstinence (Marchant et al., 2014). A recent study demonstrated that stimulating the medial NAshell-to-lateral hypothalamus pathway immediately prior to a PR test strongly increased responding for cocaine (Larson et al., 2015). Interestingly, the projection from the NAshell to the lateral hypothalamus is almost exclusively composed of D1 MSNs and optogenetic stimulation of the pathway strongly suppresses food intake (O'Connor et al., 2015). Both the medial NAshell and the lateral NAshell also project directly to the VTA (Watabe-Uchida et al., 2012) and projection neurons in these regions show increased Fos expression after cue-induced reinstatement of cocaine seeking. Notably, this effect was not observed in the rostral part of the ventral shell (Mahler and Aston-Jones, 2012).

The NAshell, ventromedial VP, mediodorsal thalamus, and ILC comprise a distinct limbic loop from the NAcore/dorsolateral VP/medial dorsal nucleus/PLC, and these subcircuits may drive differential motivational processes (Alexander et al., 1990; O'Donnell et al., 1997). Although the mediodorsal thalamus might not be directly involved in drug-seeking responses (McFarland and Kalivas, 2001; McFarland et al., 2004), recent data show involvement of this loop in reward-related learning processes (Leung and Balleine, 2013, 2015), suggesting that it may be involved in the initial stages of addiction.

V. Drug-Induced Plasticity

As discussed above, the NAc is a major input structure of the basal ganglia that receives inputs from many

brain regions (Voorn et al., 2004; Stuber et al., 2012; Britt and Bonci, 2013; Gipson et al., 2014), and the MSNs of the NAc are relatively hyperpolarized with low spontaneous activity and therefore depend on excitatory glutamatergic transmission to activate (O'Donnell and Grace, 1993; Peoples and West, 1996). Release of glutamate into the synapse causes the activation of two primary types of ionotropic glutamate receptors: the AMPARs and the NMDARs. The efficiency of glutamate neurotransmission on MSN activity depends on two main factors. First, the probability of presynaptic glutamate release is generally determined by Ca^{2+} levels in the axon terminals (Katz and Miledi, 1965, 1967) after an action potential but is also modulated by other factors (Blackmer et al., 2001; Photowala et al., 2006; Kupchik et al., 2011a). A higher probability of release equates with stronger synaptic contact and can be identified by a higher frequency of sEPSCs or miniature excitatory postsynaptic currents (mEPSCs) or by alteration of the paired-pulse ratio (PPR), which is the ratio between the amplitudes of two consecutive excitatory postsynaptic currents (EPSCs). Second, postsynaptic sensitivity to released glutamate is determined by the number and type of postsynaptic receptors. Increased receptor density allows glutamate to generate larger amplitude currents and is generally measured as an increase in the amplitude of sEPSCs/mEPSCs, lack of a change in PPR, or an increase in the ratio between currents produced by AMPARs and NMDARs (AMPA/NMDA). Importantly, changes in the type of channels or their subunits, as discussed below, can alter influx of different ions and therefore engage different cellular processes.

In this section, we discuss the long-term neuroplasticity caused at glutamatergic synapses in the NAc after exposure to drugs of abuse and the suggested underlying mechanisms, as well as newer findings showing rapid and transient neuroplasticity induced by drug-associated cues. In addition, we review recent studies using transgenic mice showing that drug-induced synaptic plasticity in the NAc can be limited to specific inputs and to specific types of MSNs.

A. Long-Term Synaptic Plasticity

One of the more robust features of addiction is the enduring propensity to relapse. This persistent state was long hypothesized to be encoded by synaptic changes in the mesolimbic system. Indeed, early work in the VTA shows synaptic adaptations occurring after exposure to cocaine or morphine (Bonci and Williams, 1996, 1997; Ungless et al., 2001; Thomas et al., 2008). However, the desire to use drugs is encoded in glutamatergic synapses of the NAc (Kalivas, 2009). The best established data set for drug-induced synaptic plasticity in the NAc is after cocaine use. A single noncontingent injection of cocaine does not produce any synaptic changes in excitatory transmission in the NAc, whereas repeated injections cause a depression of EPSCs (Thomas et al., 2001; Kourrich et al., 2007; Huang et al., 2009; Ortinski et al., 2012). A similar depression is also seen after self-administrated cocaine (Schramm-Sapyta et al., 2006). Interestingly, a period of withdrawal from cocaine leads to potentiation of excitatory input, be it after a single cocaine injection (Pascoli et al., 2012), repeated cocaine injections (Kourrich et al., 2007; Britt et al., 2012), cocaine self-administration (Gipson et al., 2013a; Pascoli et al., 2014), or during the incubation of craving (Conrad et al., 2008).

Evidence for other addictive drugs is not complete and at times shows opposite changes in the NAc compared with cocaine. For example, withdrawal from nicotine self-administration shows a similar potentiation (Gipson et al., 2013b), whereas the results are mixed for studies examining the NAc after withdrawal from heroin exposure (Russo et al., 2010; Shen et al., 2011; Wu et al., 2012). Chronic ethanol induces an increase in mEPSC frequency with no change in amplitude; however, mEPSC frequency is decreased and mEPSC amplitude is increased after withdrawal, indicating that two opposing mechanisms are activated (Spiga et al., 2014). Regardless of the specific change and the specific model used, these data support the perspective that the enduring symptoms of drug addiction may be encoded by synaptic changes in the NAc.

1. Long-Term Depression. The first electrophysiological evidence for LTD in the NAc was found by Pennartz et al. (1993). In this study, tetanic stimulation produced LTD of AMPA currents in a minority of the cells that did not depend on the activation of NMDARs. One year later, Kombian and Malenka (1994) showed that tetanic stimulation of the glutamatergic input to the NAc, as well as a low-frequency stimulation paired with depolarization of the recorded MSN, caused an LTD of NMDA currents (they did not report an LTD in the AMPA currents). Over the years, several types of LTD mechanisms have been described in the NAc that are relevant in addiction. Except for the NMDA-dependent LTD described above, the major LTD mechanisms include activation of mGluRs and endocannabinoid receptors, but reports also revealed involvement of dopaminergic and opioid receptors in inhibiting glutamatergic neurotransmission onto MSNs in the NAc.

a. Metabotropic glutamate receptor 2/3–dependent long-term depression. Although the immediate consequence of glutamate synaptic release is the transient activation of the ionotropic channels, released glutamate can exert long-lasting effects through activation of another class of glutamatergic receptors, the mGluRs (Niswender and Conn, 2010). See section VI for an overview of pharmacological manipulations on mGluRs. mGluRs are G protein–coupled receptors that are divided into three groups. Group I consists of mGluR1 and mGluR5 and is predominantly expressed postsynaptically. Group II consists of mGluR2 and mGluR3, which

are predominantly expressed presynaptically. Group III consists of mGluR4 and mGluR6– mGluR8, which are also largely presynaptic. Of these, group II and III mGluRs are inhibitory autoreceptors on glutamatergic terminals (Conn and Pin, 1997; Testa et al., 1998; Niswender and Conn, 2010; Kupchik et al., 2011b) and heteroreceptors on dopaminergic (Hu et al., 1999; Karasawa et al., 2006) and GABAergic terminals (Kosinski et al., 1999; Karasawa et al., 2006; Mao et al., 2013; Tang et al., 2013). The heteroreceptors will not be further discussed here (for review, see Mao et al., 2013). As autoreceptors, group II and III mGluRs are localized mostly just outside, at the annulus of the synaptic cleft, although they have been reported to exist also inside the synaptic cleft (Petralia et al., 1996; Shigemoto et al., 1997; Tamaru et al., 2001). These receptors regulate glutamate neurotransmission through various pathways, including activation of presynaptic K^+ channels (Anwyl, 1999), inhibition of presynaptic Ca^{2+} channels (Anwyl, 1999; Robbe et al., 2002a), and direct interaction with the release machinery (Kupchik et al., 2008, 2011b).

Both group II and III mGluRs are expressed in the NAc (Pisani et al., 1997; Testa et al., 1998; Robbe et al., 2002b; Xi et al., 2002; Moussawi and Kalivas, 2010) but since their discovery, research in the NAc has focused mainly on the effects of group II mGluRs on glutamate synaptic transmission. Pharmacological activation of mGluR2/3 or group III mGluRs in the NAc inhibits glutamate synaptic transmission (Manzoni et al., 1997; Robbe et al., 2002b) and is accompanied by a change in the PPR and frequency of mEPSCs, indicating a presynaptic mechanism by mGluRs directly on glutamatergic presynaptic terminals (Robbe et al., 2002a). Tetanic stimulation–induced mGluR2/3 LTD does not depend on activation of NMDA channels (Pennartz et al., 1993) but is mediated by a long-lasting decreased contribution of presynaptic P/Q calcium channels to glutamate release (Robbe et al., 2002a). In addition, mGluR2/3 appears to be under tonic activation in control conditions. Microdialysis experiments show that infusion of the mGluR2/3 antagonist LY341495 (2-[(1*S*,2*S*)-2-carboxycyclopropyl]-3-(9*H*-xanthen-9-yl)-D-alanine) increased baseline levels of glutamate (Xi et al., 2002; Moussawi and Kalivas, 2010), whereas the same antagonist caused an increase in evoked EPSC amplitude (Moussawi et al., 2011; Kupchik et al., 2012; although see Moran et al., 2005).

Exposure to drugs of abuse alters the regulation of glutamate neurotransmission by group II mGluRs. Chronic treatment with morphine, a μ-opioid receptor ligand, followed by short withdrawal enhances the mGluR2/3-mediated, but not the group III–mediated, inhibition of NMDA currents in the NAc through a presynaptic mechanism (Martin et al., 1999). In contrast, prolonged withdrawal from chronic cocaine (Moussawi et al., 2009, 2011) or morphine (Robbe et al., 2002b) causes a decrease in mGluR2/3-mediated inhibition of AMPA-mediated EPSCs. These effects are of presynaptic origin as well. Note that in the case of cocaine, the decrease in mGluR2/3 function may be a result of extinction training rather than cocaine use itself, since mGluR2/3 LTD remains unaltered after prolonged cocaine use (40–50 days) with no withdrawal (Kasanetz et al., 2010).

A robust feature of glutamatergic PFC-NAc synapses is the loss of the ability to induce electrically stimulated mGluR2/3 LTD after withdrawal from cocaine self-administration (Moussawi et al., 2009). In drug-naïve rats, in vivo stimulation of the PLC leads to LTD that is blocked by mGluR2/3 antagonists (Moussawi et al., 2009). After cocaine self-administration and extinction, the same protocol no longer induces LTD. This may be a result of a change in the baseline activity of the mGluR2/3; whereas mGluR2/3 is tonically activated in naïve or yoked-saline rats (Moussawi et al., 2011; Kupchik et al., 2012), the tonic activation is removed after extinction of cocaine self-administration (Moussawi et al., 2011), presumably because of a reduction in extracellular glutamate levels (Baker et al., 2003; Kalivas, 2009). Normalization of extracellular glutamate levels using *N*-acetylcysteine (NAC) restores the ability to electrically induce LTD in the NAc (Moussawi et al., 2009) and this is blocked by mGluR2/3 antagonists (Moussawi et al., 2011). Importantly, NAC treatment or mGluR2/3 agonists reduce reinstated cocaine seeking (Baker et al., 2003; Zhou and Kalivas, 2008; Moussawi et al., 2009). Although reduced extracellular glutamatergic tone is selective for cocaine-withdrawn animals, increased activator of G protein (AGS) 3 may offer a more general mechanism for reduced mGluR2/3 LTD induced by different addictive drugs. AGS3 decreases Gi signaling through mGluR2/3 and other Gi-coupled receptors by competing with $\beta\gamma$ for the Giα subunit and is upregulated by cocaine, heroin, and alcohol in the PLC-accumbens projection (Bowers and Hoffman, 1986; Kalivas et al., 2003; Bowers et al., 2004, 2008; Yao et al., 2005). Thus, elevated AGS3 reduces the capacity of presynaptic mGluR2/3 to inhibit glutamate release probability (Kalivas et al., 2005). Importantly, inhibiting AGS3 prevents alcohol, cocaine, and heroin reinstatement. In conclusion, group II and III mGluRs inhibit glutamatergic neurotransmission in the NAc through decreasing the probability of vesicle release in glutamatergic terminals. Thus far, only the mGluR2/3-mediated inhibition was shown to change after exposure to drugs of abuse, and its long-term changes cause a loss in the ability to produce LTD in the NAc. This may underlie the inability of addicts to change their behavior and resist the desire to relapse, since only the subgroup of rats that most persistently press for cocaine sustain the loss of LTD after months of cocaine use (Kasanetz et al., 2010, 2013).

b. Endocannabinoid-dependent long-term depression. Marijuana is a drug that acts in the brain by activating cannabinoid (CB) 1 receptors (Lupica and Riegel, 2005;

Fratta and Fattore, 2013; Hoffman and Lupica, 2013), which are also activated by endogenous cannabinoids (eCBs). Stimulating CB1 receptors can affect neurotransmission and interestingly augment signaling of many types of neurotransmitters (Szabo and Schlicker, 2005). When secreted, eCBs originate from the postsynaptic neuron and travel retrogradely to the presynaptic terminal, activate CB1 receptors, and cause a decrease in glutamate release probability (Lupica and Riegel, 2005; Szabo and Schlicker, 2005; Hoffman and Lupica, 2013). Recent studies also support a role for astroglial CB1 receptors in the enhancement of glial glutamate release, which can modulate plasticity in adjacent synapses (Navarrete and Araque, 2008; Rossi, 2012; Hwang et al., 2014).

Activation of the CB1 receptors by the agonist WIN 55,212-2 [(*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-napthalenylmethanone] in the NAc results in a dose-dependent inhibition of glutamatergic EPSCs (Hoffman and Lupica, 2001; Robbe et al., 2001). This inhibition is, as described above, due to a presynaptic mechanism (although for a possible postsynaptic mechanism, see Hoffman and Lupica, 2001) since the frequency of mEPSCs is decreased and the PPR is increased (Robbe et al., 2001, 2003; Hoffman and Lupica, 2013). More specifically, eCBs activate a cAMP/PKA cascade in the presynaptic terminal (Mato et al., 2008) by binding to the CB1 receptor. This leads to the opening of presynaptic K^+ channels that hyperpolarize the terminals and reduce the probability of glutamate release (Robbe et al., 2001).

Apart from the direct pharmacological effect of cannabinoids on glutamate neurotransmission, tetanic electrical stimulation of NAc afferents (13 Hz for 10 minutes) induces LTD that depends on activation of CB1 receptors (eCB LTD) (Robbe et al., 2002c; Hoffman et al., 2003; Fourgeaud et al., 2004; Mato et al., 2004, 2005, 2008). Glutamate released by tetanic stimulation activates postsynaptic mGluR5, which in turn leads to a Gq-dependent increase in intracellular Ca^{2+} in the postsynaptic MSN (Lüscher and Huber, 2010). The increased intracellular Ca^{2+} leads to release of eCBs from the postsynaptic cell and these eCBs activate presynaptic CB1 receptors to inhibit glutamate release (McCutcheon et al., 2011a; Hoffman and Lupica, 2013) or CB1-expressing fast-spiking interneurons in the NAc (Winters et al., 2012). This mechanism was suggested in a recent study to affect only MSNs expressing the D2-dopamine receptor (Grueter et al., 2010), similar to the dorsal striatum (Gerdeman et al., 2002; Lüscher and Huber, 2010). In addition, the same protocol that leads to eCB LTD can also lead to forms of postsynaptic LTD (Grueter et al., 2010; Huang et al., 2011; Huang and Hsu, 2012). These include activation of postsynaptic transient receptor potential cation channel subfamily V member 1 channels that lead to internalization of AMPARs (Brebner et al., 2005) and subsequent LTD (Grueter et al., 2010) and activation of NMDA to induce calmodulin-dependent protein kinase II (CaMKII)–dependent LTD (Huang and Hsu, 2012). Both of these postsynaptic LTD forms are absent after exposure to cocaine (Grueter et al., 2010; Huang et al., 2011), suggesting relevance in cocaine addiction.

Acute single exposure to THC (Mato et al., 2004), the active ingredient in marijuana, or to cocaine (Fourgeaud et al., 2004) abolishes eCB LTD in the NAc 24 hours after the last injection. The impaired LTD is transient since eCB-mediated LTD is restored 1 week after the last injection. More chronic exposure to cannabinoids or cocaine also resulted in the loss of eCB LTD 30 minutes after the last injection (Hoffman et al., 2003) or after a longer period of withdrawal (McCutcheon et al., 2011a). However, the possibility that loss of eCB LTD induced by chronic THC is a long-lasting phenomenon or is reversed akin to after a single acute injection was not investigated. The mechanism of eCB-LTD impairment, at least by a single cocaine injection, involves downregulation of postsynaptic mGluR5 achieved by a yet-unknown mechanism that involves the activation of D1 dopamine and NMDARs (Fourgeaud et al., 2004).

c. N-methyl-D-aspartic acid–dependent long-term depression. A third form of LTD plasticity in the NAc can be achieved by coupling a low-frequency stimulation of the NAc afferents (1–5 Hz) with depolarization of MSNs to −50 mV (Thomas et al., 2000, 2001). This type of LTD is independent of mGluR or dopamine receptor activation and requires NMDAR activation and increases in postsynaptic Ca^{2+} concentrations (Thomas et al., 2000). A significant difference between mGluR2/3 LTD or eCB LTD and NMDA LTD is that the NMDA LTD is of postsynaptic origin (Thomas et al., 2001). Activation of postsynaptic NMDARs by low-frequency stimulation of afferents presumably leads to a reduction of synaptic AMPARs (Thomas et al., 2001; Kauer and Malenka, 2007). This postsynaptic mechanism may be the one underlying the synaptic depression observed after five acute injections of cocaine (Kourrich et al., 2007), although this synaptic depression may be a result of a more complicated interaction between several brain regions since NMDA LTD is independent of dopamine action in the NAc.

Akin to other forms of LTD in the NAc, LTD induced by a low-frequency stimulation is also affected by exposure to drugs. Reduction of this form of LTD was shown after repeated noncontingent cocaine injections (Thomas et al., 2001), cocaine self-administration (Martin et al., 2006; Moussawi et al., 2009; Kasanetz et al., 2010), ethanol consumption (Jeanes et al., 2011, 2014; Spiga et al., 2014), and heroin self-administration (Shen and Kalivas, 2013). Interestingly, the reduction in LTD is long-lasting in the NAcore and is also observed after 21 days of abstinence from cocaine

self-administration (Martin et al., 2006). In the NAshell, the loss of LTD was observed after 1 day, but not 21 days, of abstinence (Martin et al., 2006). However, with noncontingent injections of cocaine, the loss of LTD in the NAshell seems to last longer and was also observed after 10–14 days of abstinence (Thomas et al., 2001).

d. Dopamine and long-term depression. Glutamate release in the NAc is also modulated by the dopaminergic system. Application of dopamine on NAc slices inhibits glutamate neurotransmission through activation of D1 (Pennartz et al., 1992; Nicola et al., 1996; Harvey and Lacey, 1997; Li and Kauer, 2004; Ortinski et al., 2012) or D2 dopamine receptors (O'Donnell and Grace, 1994; Brady and O'Donnell, 2004). The depression seems to be of presynaptic origin in both cases, because mEPSC frequency, but not amplitude, is reduced (Pennartz et al., 1992; Nicola et al., 1996; but see Ortinski et al., 2012 for effects after withdrawal from cocaine) although no changes in postsynaptic cell parameters are observed (O'Donnell and Grace, 1994). This inhibition is also produced by endogenous dopamine (Harvey and Lacey, 1996; Brady and O'Donnell, 2004) and is observed by washing cocaine or amphetamine directly on the slice (Nicola et al., 1996; Li and Kauer, 2004; Wang et al., 2012). Although evidence indicates that the D1 receptors mediating the inhibition are presynaptic (Pennartz et al., 1992; Nicola et al., 1996; Nicola and Malenka, 1997), it has been suggested that the presynaptic alterations are a consequence of the interaction between postsynaptic D1 receptors and NMDARs, which causes the release of adenosine that affects the presynaptic terminal (Harvey and Lacey, 1997; Chergui and Lacey, 1999; Wang et al., 2012). Similarly, D2 receptor–mediated inhibition is thought to include postsynaptic release of eCBs, thereby pointing to a role for postsynaptic D2 receptors (Wang et al., 2012).

Evidence for drug exposure disrupting dopamine-mediated inhibition of glutamate transmission is sparse. However, withdrawal from amphetamine has been shown to abolish dopamine-mediated inhibition of NAc excitatory synapses (Li and Kauer, 2004) by an unknown mechanism. In addition, a recent study from our group shows that acute cocaine-induced synaptic plasticity in the NAc is blocked by either inhibition of the VTA or the systemic injection of a cocktail of D1 and D2 receptor antagonists (Shen et al., 2014a). Although these two studies indicate some role for dopamine in the synaptic changes occurring in the NAc after drug exposure, additional research is required.

e. Opioids and long-term depression. The NAc is rich with opioid neuropeptides and receptors expressed both pre- and postsynaptically (Mansour et al., 1988, 1995; McGinty, 2007; Chartoff and Connery, 2014). Unfortunately, despite the fact that heroin acts on μ-opioid receptors, not much is known about the role of opioids in modulating glutamate neurotransmission in the NAc. Activation of μ-opioid receptors inhibits electrically evoked AMPA and NMDA currents through a presynaptic mechanism (Martin et al., 1997; Hoffman and Lupica, 2001) that involves reduction of terminal calcium influx (Martin et al., 1997). Interestingly, when NMDA is superfused over the slice, the generated postsynaptic NMDA current is potentiated by activation of μ-opioid receptors (Martin et al., 1997). The same NMDA potentiation is observed after heroin self-administration and extinction or after a heroin challenge in a heroin-extinguished rat, presumably by an increase in the NMDA containing the GluN2B subunit (Shen et al., 2011), and a reduction in GLT-1, allowing glutamate to spill out of the synapse and activate extrasynaptic GluN2B receptors (Shen et al., 2014b). These opioid-driven changes in NMDA function are crucial for drug-seeking behavior, because blocking opioid-induced NMDA changes attenuates relapse to heroin (Shen et al., 2011). Dynorphin also inhibits accumbens glutamate release in two parallel pathways (Mu et al., 2011). Dynorphin A inhibits glutamate transmission through activation of κ-opioid receptors, whereas dynorphin B acts in a κ-independent manner. Interestingly, only the κ-dependent inhibition was abolished by cocaine exposure. Clearly, more research is required to understand whether and how opioid modulation of glutamate transmission in the NAc is involved in drug addiction.

2. Long-Term Potentiation. After exposure and withdrawal from several types of drugs (Kourrich et al., 2007; Britt et al., 2012; Ortinski et al., 2012; Pascoli et al., 2012; Gipson et al., 2013a,d; Shen et al., 2014a), a persistent potentiation of glutamatergic input into the NAc is observed. Several mechanisms have been described as potentially underlying the drug-induced LTP. Below we review these mechanisms.

a. N-methyl-D-aspartic–dependent long-term potentiation. High-frequency stimulation of NAc afferents leads to LTP (Pennartz et al., 1993; Kombian and Malenka, 1994; Kauer and Malenka, 2007; Moussawi et al., 2009; Pascoli et al., 2012). As in other brain regions (Bliss and Lomo, 1973; Malenka and Bear, 2004), this form of LTP in the NAc requires activation of postsynaptic NMDARs, entry of Ca^{2+} into the spine, activation of protein kinases including CaMKII (Malenka and Nicoll, 1999; Kauer and Malenka, 2007) and ERK (Bertran-Gonzalez et al., 2008; Pascoli et al., 2012), and insertion of new AMPARs into the postsynaptic membrane. How exposure to drugs elicits this LTP is still not entirely understood. An important finding is that this potentiation does not occur during the drug use but requires a period of withdrawal (Kourrich et al., 2007; Wu et al., 2012). In fact, the glutamatergic synapses in the NAc are depressed immediately after exposure to cocaine or morphine (Kourrich et al., 2007; Mameli et al., 2009; Wu et al., 2012). Thus, it was suggested that the observed potentiation after withdrawal

is attributable to synaptic scaling (Turrigiano and Nelson, 2000), a compensatory upregulation of synaptic strength due to the chronic depression caused by repetitive drug exposure (Boudreau and Wolf, 2005). Accordingly, a general decrease in neuronal excitability in the NAc after exposure to drugs (Zhang et al., 1998, 2002; Hu et al., 2004; Dong et al., 2006), together with chronic changes in extracellular glutamate (Kalivas, 2009), may trigger events leading to a compensatory potentiation of the glutamatergic synapses. Another hypothesis, which is discussed below, suggests that exposure to cocaine generates silent synapses in the NAc, which can explain both the decrease in synaptic strength during drug self-administration and the potentiated state after withdrawal (Lee and Dong, 2011).

LTP induced by high-frequency stimulation is impaired after withdrawal from cocaine (Moussawi et al., 2009) or heroin (Shen et al., 2011; Wu et al., 2012). In the case of cocaine, this may be the result of a masking effect, because the synapses are already potentiated after withdrawal from cocaine (Kourrich et al., 2007; Gipson et al., 2013a). However, the mechanism for heroin is unknown, since, unlike cocaine, withdrawal from heroin does not constitutively strengthen glutamatergic synapses in the NAc (Shen et al., 2011). The loss of the ability to induce LTP is tightly linked to drug-seeking behavior, since rescuing LTP leads to a significant decrease in reinstatement of cocaine-seeking behavior (Moussawi et al., 2009). Despite the above, it is important to note that although the experimenter-induced LTP is impaired, the system is still capable of changing. Accordingly, a drug challenge after a period of withdrawal causes depression (Thomas et al., 2001; Kourrich et al., 2007), whereas introduction of a drug-associated cue induces a rapid potentiation (Gipson et al., 2013a) of glutamatergic synapses in cocaine-withdrawn rats. Thus, although the classic, NMDA-dependent LTP is impaired in drug-experienced animals, other LTP mechanisms may participate in drug-induced changes after withdrawal.

b. Calcium-permeable α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors. LTP involves insertion of AMPARs into the postsynaptic membrane. This does not necessarily mean that the inserted AMPARs are of the same type as those that already exist in the synapse. AMPARs are composed of different subunits and can have different properties depending on the subunit composition. Specifically, AMPARs that contain the GluA2 subunit have poor Ca^{2+} conductance or are Ca^{2+} impermeable (CI), whereas the receptors lacking the GluA2 subunit are CP (Wolf and Tseng, 2012). The latter are easily identified electrophysiologically because they have poor outward ion conductance when depolarized and are thus termed as inwardly rectifying (Hume et al., 1991; Burnashev et al., 1992; Hollmann and Heinemann, 1994; Conrad et al., 2008). Two tools are commonly used for the electrophysiological identification of CP-AMPARs: 1) application of Naspm, a specific CP-AMPAR blocker; and 2) measurement of AMPAR-mediated EPSCs after hyperpolarization (e.g., −70 mV) and depolarization (e.g., +40 mV) to generate a rectification index. Changes in the rectification index indicate a change in the stoichiometry of CP-AMPARs. Drug-naïve animals express almost exclusively the CI-AMPARs in the NAc (Kourrich et al., 2007; Mameli et al., 2009; Grueter et al., 2010; Shen et al., 2014a; although see Campioni et al., 2009). The effects of drug exposure are complex and appear to depend on the animal model employed. Noncontingent injections of cocaine cause an increase in CI-AMPARs, regardless of withdrawal time (McCutcheon et al., 2011b). This is also the case when the limited-access model (2 hours per day) is used (Purgianto et al., 2013). When the extended access model is used (Ahmed and Koob, 1998), CP-AMPARs are inserted into the postsynaptic membrane after about 25 days or more of withdrawal (Conrad et al., 2008; Mameli et al., 2009; Ferrario et al., 2011; McCutcheon et al., 2011a,b; Wolf and Tseng, 2012), as indicated by an increase in the rectification index and by increased inhibition by Naspm. The increase in synaptic CP-AMPARs appears to depend on constant protein translation, because disruption of protein translation restored the baseline rectification index and abolished the effect of Naspm (Scheyer et al., 2014), and the increase in CP-AMPARs seems to occur specifically in afferents from the amygdala (Lee et al., 2013) and the IFC (Ma et al., 2014). High synaptic CP-AMPAR levels are important for generating drug-seeking behavior, because microinjections of Naspm into the NAc (Conrad et al., 2008) or reversing CP-AMPAR accumulation (Lee et al., 2013; Loweth et al., 2014; Ma et al., 2014) reduces cue-induced cocaine seeking, whereas increasing CP-AMPAR levels in the NAc enhances drug-seeking behavior (Briand et al., 2014). The series of events required for insertion of CP-AMPARs is not yet fully clear. Several lines of evidence point to an mGluR1-dependent insertion of CP-AMPARs into silent synapses. For example, it has been proposed that CP-AMPARs are inserted into the postsynaptic membrane as part of the process of unsilencing silent synapses (Ma et al., 2014). It has been proposed that the insertion process may be triggered by an mGluR1-dependent mechanism since mGluR1 activation in cocaine-withdrawn rats causes internalization of CP-AMPARs and insertion of new CI-AMPARs into the synapse (McCutcheon et al., 2011a). Indeed, a decrease in mGluR1 precedes the accumulation of CP-AMPARs, and restoring mGluR1 function by a positive allosteric modulator prevented CP-AMPAR accumulation and decreased craving for cocaine (Loweth et al., 2014). The decrease in mGluR1 function may or may not be linked to a decrease in the function of the glutamate receptor interaction protein, a protein that incorporates GluA2-containing AMPARs into the membrane, because glutamate receptor interaction

protein knockout mice show an altered rectification index, a loss of LTD, and increased drug-seeking behavior (Briand et al., 2014). The mechanistic link between cocaine use and the decrease in mGluR1 function is still to be found. A possible component may be VTA activity, since mice lacking NMDARs on dopamine cells do not show increased synaptic CP-AMPAR levels in the NAc after withdrawal (Mameli et al., 2009). This and other avenues still must be investigated.

c. Silent synapses. An emerging potential mechanism for the synaptic potentiation after withdrawal from drug use is embodied in the silent synapse hypothesis of addiction (Lee and Dong, 2011). Silent synapses (Merrill and Wall, 1972) are a unique type of glutamatergic synapse that expresses mostly NMDARs with little, if any, AMPARs (Liao et al., 1995; Isaac et al., 1999; Hanse et al., 2009). Thus, when the proportion of silent synapses on a single MSN increases, the recorded EPSC shows decreased average amplitude with higher variance in the amplitude between stimulations (measured as the coefficient of variation of the EPSC amplitude). Huang et al. (2009) used this measure to show that noncontingent cocaine injections produced "de novo" silent synapses by loading GluN2B-containing NMDARs into new synaptic sites in a CREB-mediated pathway (Brown et al., 2011b). After cocaine withdrawal, these new silent synapses mature by recruiting AMPARs and potentiate the overall AMPAR-mediated current onto the cell (Huang et al., 2009; Lee and Dong, 2011; Ma et al., 2014). Interestingly, maturation of the cocaine-induced silent synapses after prolonged withdrawal involves insertion of CP-AMPARs into the synapse, thus providing a possible mechanism underlying incubation of cocaine craving (Ma et al., 2014). This was not found in all MSNs, but mainly in those receiving input from the infralimbic cortex (MSNs receiving prelimbic input were unsilenced by insertion of CI-AMPARs). In addition, there seems to be specificity for the generation of silent synapses when it comes to the type of MSN. In a work examining the role of ΔFosB in cocaine addiction, overexpression of ΔFosB increased the proportion of silent synapses on D1-MSNs but decreased it in D2-MSNs (Grueter et al., 2013). Likewise, Koya et al. (2012) showed that silent synapses are generated after cocaine sensitization only in a minority of neurons that show increased Fos expression in the NAc. Overall, silent synapses may play a significant role in potentiating glutamatergic input into the NAc after withdrawal and the incubation of craving in rats with cocaine self-administration experience. However, the generation and maturation of silent synapses seems to be cell type specific and circuit specific. Similarly, given the lack of constitutive potentiation of synapses after withdrawal from heroin, it will be of interest to determine whether silent synapse formation is necessary for heroin addiction.

3. Afferent– and Medium Spiny Neuron–Specific Synaptic Plasticity. Being the main input structure of the ventral basal ganglia, the NAc receives glutamatergic input from multiple sources (Stuber et al., 2012; Britt and Bonci, 2013; Gipson et al., 2014), including the PFC, amygdala, hippocampus, thalamus, and VTA. However, interrogating synaptic plasticity in specific afferents or cell types of the NAc became possible only in recent years after the introduction of optogenetic (Boyden et al., 2005) and chemogenetic (Sternson and Roth, 2014) tools. It is becoming clear that different inputs into the NAc, as well as the different MSN types, show different drug-induced forms of plasticity and electrically induced EPSCs may not reveal those changes and generate conflicting results. For instance, many studies show that drug-induced changes in the PPR were not paralleled by changes in the frequency of mEPSCs even though both parameters are indicators of presynaptic changes (Dobi et al., 2011; Moussawi et al., 2011; Wu et al., 2012). The source for this discrepancy is presumably the fact that the PPR is measured from a limited number of synapses stimulated electrically, whereas the mEPSCs that converge onto the recorded MSN originate in all input regions. Deciphering the specific neural circuits that underlie addictive behavior has become the focus of current research, and below we review the relevant literature.

a. Afferent-specific synaptic plasticity.

i. Prefrontal Cortext to the Nucleus Accumbens. PFC efferents to the NAc have been long proposed to undergo synaptic plasticity after drug exposure. This was based mainly on in vivo stimulation or inactivation of the PFC and subsequent detection of changes in the NAc (for review, see Kalivas, 2009). However, the first direct demonstration of drug-induced changes in the corticoaccumbal synapse was provided by Pascoli et al. (2012), who showed that NMDA-dependent LTD in the ILC-NAshell synapses is augmented after a single cocaine injection followed by 1 week of withdrawal. This group further explored the connectivity between the mPFC and accumbens and found that only mPFC input onto D1 MSNs, but not D2 MSNs, shows cocaine-induced synaptic changes (Pascoli et al., 2014). These changes include alterations in NMDA LTD and mGluR2/3 LTD and an increase in the rectification index, indicating recruitment of CP-AMPARs into those synapses. Similar CP-AMPAR insertion into the ILC-NAshell synapse was also found in the cocaine incubation model (Ma et al., 2014). Interestingly, the PLC-NAc core synapses showed insertion of CI-AMPARs, and reversing the maturation process in both pathways gained opposing behavioral outcome. In contrast, Britt et al. (2012) showed that if cocaine is injected in a noncontingent manner, no change is observed in the AMPA/NMDA in PFC-NAc synapses. In addition, Terrier et al. (2016) showed that CP-AMPARs are specifically inserted in mPFC-to-D1 MSN synapses after high-dose cocaine self-administration and 30 days of withdrawal. Finally, cocaine-induced presynaptic alterations were also found in the PFC-NAc synapse (Suska

et al., 2013). In this study, short-term (1 day) or long-term (45 days) withdrawal led to an increase in the probability of release from the PFC, but not from BLA terminals.

ii. Basolateral Amygdala to the Nucleus Accumbens. BLA glutamatergic input into the NAc is rewarding (Stuber et al., 2011) and is strongly implicated in cue-induced reward-seeking behavior (Setlow et al., 2002; Di Ciano and Everitt, 2004; Ambroggi et al., 2008; Mashhoon et al., 2010; Shiflett and Balleine, 2010; Stuber et al., 2011; Stefanik and Kalivas, 2013). Thus, recent research has focused on the synaptic changes occurring in the BLA-NAc synapses after drug exposure. MacAskill et al. (2014) found that the number of BLA connections with NAc D1-MSNs, but not D2-MSNs, was increased after repeated noncontingent cocaine injections. In the incubation model, on the other hand, these synapses show postsynaptic changes (Lee et al., 2013). One day after cocaine self-administration, the BLA-NAc projection shows an increase in silent synapses and those synapses mature after 45 days of withdrawal by insertion of postsynaptic CP-AMPARs. In contrast with what has been reported for the mPFC, there is a specific insertion of CP-AMPARs into synapses in the BLA to D2 receptor to MSN pathway after withdrawal from high-dose cocaine self-administration (Terrier et al., 2016). Other studies, however, did not find any alterations in the BLA-NAc after noncontingent cocaine injections (Britt et al., 2012) or cocaine self-administration (Pascoli et al., 2014) or in the incubation model (Suska et al., 2013).

iii. Ventral Hippocampus to the Nucleus Accumbens. In the medial NAshell, the focus of many of the above studies, the main glutamatergic input originates in the vHPC (Britt et al., 2012). This projection potentiates after withdrawal from noncontingent (Britt et al., 2012) or contingent (Pascoli et al., 2014) cocaine. In the latter case, the potentiation was specific to input onto D1 MSNs. In contrast, repeated noncontingent cocaine injection followed by a short (3-day) withdrawal resulted in depression of vHPC input onto D1 MSNs (MacAskill et al., 2014). This depression is mediated by presynaptic and postsynaptic mechanisms.

b. Dopamine receptor 1 medium spiny neuron– and dopamine receptor 2 medium spiny neuron–specific changes. The use of transgenic mice allows recording from identified MSNs in the NAc. This led to several interesting discoveries with respect to synaptic changes leading to addictive behaviors. In general, most studies show that exposure to cocaine, irrespective of the behavioral model, potentiates excitatory input onto D1 MSNs but not D2 MSNs (Bertran-Gonzalez et al., 2008; Dobi et al., 2011; Pascoli et al., 2012; Bock et al., 2013; MacAskill et al., 2014). In contrast, overexpression of ΔFosB increased behavioral responses to cocaine but decreased excitatory input onto D1 MSNs (Grueter et al., 2013). This was explained by an increase in silent synapses. Thus, the reported depression may turn into potentiation after the silent synapses mature (Lee and Dong, 2011). In addition to changes in D1 MSNs, some studies show adaptations in D2 MSNs as well. These include loss of eCB LTD (Grueter et al., 2010) and a ΔFosB-induced increase in excitatory input onto NAshell D2 MSNs and a decrease in silent synapses (Grueter et al., 2013). Interestingly, increasing the activity of D2 MSNs normalizes motivated behavior and attenuates drug-seeking behavior (Bock et al., 2013). Thus, the long-suggested opposite roles of D1 MSNs and D2 MSNs in the expression of motivated behavior (Gerfen and Surmeier, 2011) is generally supported in studies of behaviors induced by addictive drugs.

In the majority of the studies mentioned above, a conceptual link between D1 MSNs/D2 MSNs and the direct/indirect pathway, respectively, is made by relying on dorsal basal ganglia connectivity. In fact, a recent article asserts that in contrast with the dorsal portions of the striatum, the segregation of D1 MSNs and D2 MSNs in the NAc into direct and indirect pathways is much less defined (Smith et al., 2013; Kupchik et al., 2015). Because of this finding, it currently remains unclear how the selective roles of D1- and D2-expressing MSNs in the NAc may involve the classic direct and indirect pathways.

B. Short-Term Synaptic Plasticity

The long-term changes described above are all induced by past exposure to drugs. Thus, they may make the addict susceptible for relapse. Importantly, since the enduring synaptic plasticity outlined above is not induced by all addictive drugs, it may not reflect the key adaptations that underpin the engagement of drug-seeking behaviors that mediate relapse. Thus, it is possible that when an animal engages in drug-seeking behaviors, additional synaptic plasticity may occur that mediates the behavior. These changes would need to be rapidly induced, given that drug-seeking behavior can be rapidly initiated by drug-associated cues and, if relevant to the behavior, should be shared across chemical classes of addictive drug.

Substantial evidence supports the likelihood that glutamate neurotransmission in the NAc is critical for drug seeking. For example, both pharmacological (Cornish and Kalivas, 2000; Di Ciano and Everitt, 2001; Park et al., 2002; Kalivas et al., 2005) and optogenetic (Stefanik and Kalivas, 2013; Stefanik et al., 2013b) inhibition of corticoaccumbens projections attenuate the reinstatement of drug-seeking behavior. To determine whether this necessary glutamate transmission is associated with alterations in synaptic strength, we recently examined excitatory synaptic transmission in the NAcore at different times after a rat was exposed to a drug-associated cue that reinstates cocaine-seeking behavior (Gipson et al., 2013a). We found that the glutamatergic input to the NAc from the PLC, which is already potentiated during withdrawal, is further

potentiated already by 15 minutes after cue-induced reinstatement. Notably, the amount of lever presses during the reinstatement session was positively correlated with the increase in AMPA/NMDA (Gipson et al., 2013a) and this correlation is the strongest when AMPA/NMDA is correlated with the behavior during the first 5 minutes of the reinstatement session (Gipson et al., 2014). Also, akin to the behavioral response, the AMPA/NMDA ratio is back to baseline levels by the end of the 120-minute reinstatement session. Importantly, transient synaptic potentiation is also found after reinstatement of nicotine (Gipson et al., 2013b) and heroin (Shen et al., 2011) seeking. Thus, the cue-induced synaptic potentiation observed during reinstatement may be a common phenomenon across classes of addictive drugs, and thereby has the potential to provide targets for treating relapse to drug use.

C. Morphologic Plasticity

Drugs of abuse have been found to alter dendritic spine morphology on MSNs within both the NAcore and NAshell. Dendritic spines are very plastic (Nimchinsky et al., 2002), and changes in their structure are generally accepted to be strongly associated with synaptic strength since their spontaneous generation, selection, and consolidation underlie the physical foundation for learning and memory (De Roo et al., 2008; Kasai et al., 2010a,b; Dietz et al., 2012). In general, the formation of new spines or enlargement of existing spines is considered a correlate of LTP, whereas the retraction or contraction of spines is associated with LTD (Fig. 3). Measurement of dendritic spine morphologic characteristics, such as density, volume, head diameter, and neck length, involves using multiple methods that allow for either two- or three-dimensional analysis of spines on dendritic branches, including filling cells with lucifer yellow, the lipophilic dye DiI, and Golgi-Cox staining, among others (Russo et al., 2010). More recently, two-photon imaging allows for real-time visualization of spine dynamics in vivo using a cranial window (although this technique is limited to superficial layers of the neocortex) (Isshiki and Okabe, 2014; Isshiki et al., 2014). Although each method has benefits and drawbacks, visualizing dendritic spine morphology has advanced our understanding of drug-induced alterations in postsynaptic spines within addiction circuitry.

Interestingly, complex changes in excitatory neurotransmission have been found in the NAcore (Grueter et al., 2012). In addition, different drugs of abuse (e.g., heroin and cocaine) alter dendritic spine morphology differentially, such that after extended withdrawal (2 to 3 weeks) from heroin or morphine, dendritic spines quantified via density or head diameter rest in a depressed state (Robinson and Kolb, 1999; Shen et al., 2011); after withdrawal from cocaine or nicotine, spines rest in a relatively potentiated state, measured as increased density, head diameter, or neck length (Brown and Kolb, 2001; Robinson et al., 2001; Gipson et al., 2013a,b) within the NAcore or NAshell. Thus, the enduring change (increase or decrease in head diameter) in synaptic strength inferred from the morphology of dendritic spines is not consistent across different drug classes. However, in the case of heroin, nicotine, and cocaine, reinstatement of drug seeking elicits similar increases in head diameter after contingent exposure to discrete cues or environmental context associated with the drug of abuse [cocaine (Gipson et al., 2013a; Stankeviciute et al., 2014) or nicotine (Gipson et al., 2013b)] or priming of the drug itself [heroin (Shen et al., 2011) or cocaine (Shen et al., 2009, 2014a]. Thus, similar to the electrophysiological plasticity estimated by AMPA/NMDA ratios, relapse-associated increases in spine head diameter are a consistent neuroadaptation and may mediate the shared characteristic of relapse vulnerability between drug classes. In contrast, constitutive changes vary between drug classes and are less likely to underpin the shared behavioral characteristics of addiction, such as drug relapse.

Although both NAcore and NAshell MSNs show similar general changes to treatment with cocaine, detailed evaluation suggests that cocaine differentially regulates synaptic plasticity between these two subregions in distal versus proximal dendrites (Dumitriu et al., 2012). For example, at 4 hours of withdrawal from cocaine injection, proximal spine density is increased in the shell but not core. Furthermore, at 24 hours of withdrawal, an increase in proximal dendritic spine density is again found in the shell but not core. After 28 days of withdrawal, spine density in the core remained decreased but returned to baseline in the shell. In contrast with the these more subtle differences in constitutive cocaine-induced changes in spine morphology, the accumbens subcompartments diverge markedly in the induction of transient potentiation where the NAcore shows potentiation but the NAshell does not respond to a cocaine cue (Smith et al., 2014).

D. Functional Relevance of Spine Dynamics

The mechanisms by which spines grow or shrink have been extensively studied, and bigger dendritic spines have been associated with stronger dendritic contacts (Kopec and Malinow, 2006). Actin is a main structural component of dendritic spines and is organized into filaments that are associated with the plasma membrane and at the synapse. These filaments have barbed ends and are organized into long stalks that cycle to expand or contract dendritic spines (Fifková and Delay, 1982; Matus et al., 1982, 2000; Fifková and Morales, 1992). Activation of AMPARs increases head diameter (Zhao et al., 2012), and this is attributed to a stabilization of spines through actin-dependent mechanisms (Fischer et al., 2000; Richards et al., 2004). Specifically, this is thought to be due to a shift in the balance

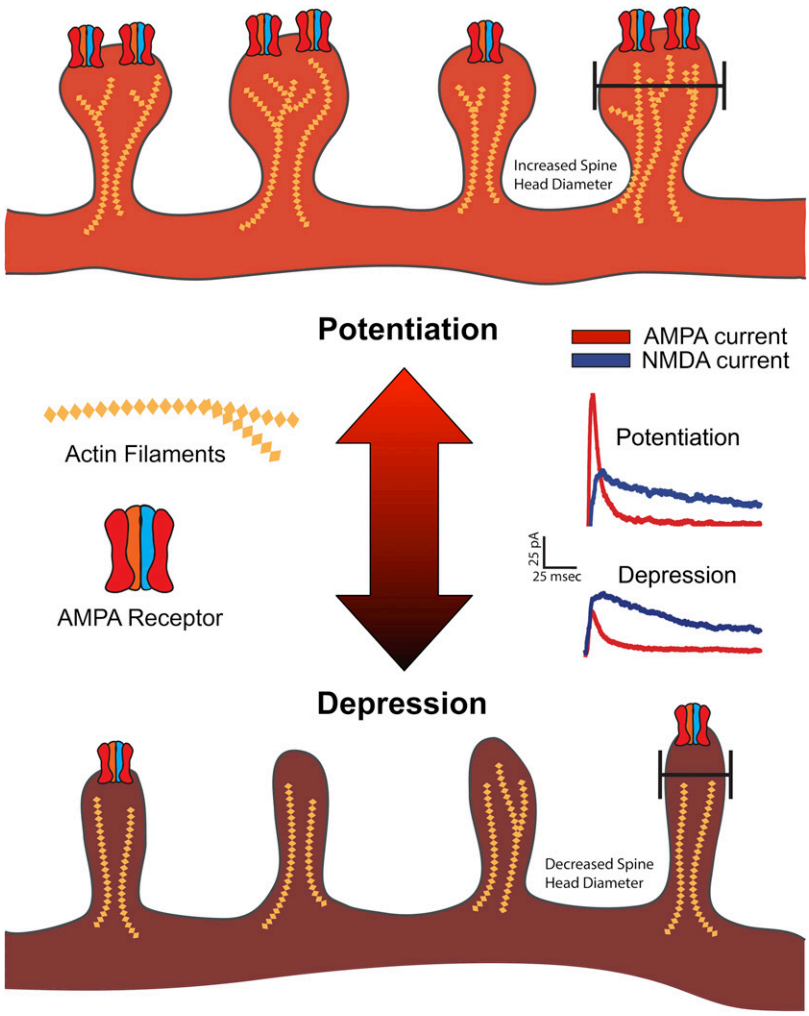

Fig. 3. Spine head diameter and synaptic potentiation. Synaptic plasticity involves both structural and functional changes that allow stronger or weaker synaptic connections. In LTP, spine head diameter increases to allow insertion of AMPARs at the synapse. The functional output of synaptic potentiation is an increase in the ratio between AMPA and NMDA EPSCs, with either more AMPA or less NMDA. For changes in spine morphology to occur, the actin cytoskeleton must grow and become more complex to allow structural growth or shrinkage. Actin cycling involves the formation of filamentous actin from the monomer (G-actin). These filaments have barbed ends and are organized into long stalks that cycle to expand or contract dendritic spines. In LTD, spine head diameter decreases and AMPARs are removed. In parallel with these structural changes, the functional reading of synaptic plasticity, the AMPA/NMDA ratio, is decreased.

between the two forms of actin: F-actin (filament) and G-actin (monomer) (Zhao et al., 2012). Indeed, remodeling of actin underlies morphologic changes in spines during synaptic plasticity, and this process constantly reshapes adult brain circuitry and connections in response to environmental stimuli; in turn, this underlies learning and memory processes. Activation of AMPARs during the induction of LTP has been shown to increase head diameter (Fischer et al., 2000), and an increase in the GluA1 subunit of the AMPAR is positively correlated with the ability of a calcium transient produced in the head of the spine to diffuse into the dendrite (Korkotian and Segal, 2007). In addition, short spines had a higher probability of raising GluA1 than long ones, indicating functional relevance for morphologic differences in spine shape, including length. The implication that morphologic changes in spines drive changes in synaptic AMPAR expression is a supported by pharmacological inhibition of F-actin altering the movement of receptors into and out of the synapse (Charrier et al., 2006; Cingolani and Goda, 2008). In addition, manipulation of F-actin via overexpression of Drebrin-A, an abundant neuron-specific F-actin binding protein, augmented glutamatergic transmission measured as a change in the amplitude and frequency of spontaneous AMPA currents in mature cultured hippocampal neurons (Ivanov et al., 2009a,b). As well, an increase in head diameter has been hypothesized to be the result of increased actin cycling and AMPAR trafficking to the cell surface (Kopec and Malinow, 2006; Kopec et al., 2006). Activation of F-actin via tetanic stimulation caused a rapid, persistent shift toward F-actin from G-actin and increased CaMKII levels. CaMKII is essential for recruiting AMPARs into the postsynaptic membrane (Okamoto et al., 2004) and is necessary for induction of NAshell dendritic spines and

behavioral sensitization to cocaine (Robison et al., 2013). Taken together, these results imply that activation of F-actin could increase AMPARs in the postsynaptic membrane, and spine enlargement may be required to allow AMPAR insertion in cocaine-induced synaptic plasticity.

Chronic cocaine or morphine exposure is associated with an increase in F-actin and actin cycling (Toda et al., 2006). Manipulation of the mechanisms of spine enlargement during withdrawal from cocaine exposure has shown that compared with saline (drug-naïve animals), animals withdrawn from chronic cocaine had elevated levels of F-actin in the NAc (both core and shell) (Shen et al., 2009). Furthermore, animals given a cocaine injection after withdrawal from chronic experimenter-delivered cocaine showed a transient but robust increase in F-actin and Arp-3 (PSD protein regulating actin cytoskeleton cycling). In addition, latrunculin A, which binds to G-actin and prevents polymerization of G-actin into F-actin, has been shown to inhibit F-actin levels proportionally to the rate of F-actin disassembly (Morton et al., 2000; Toda et al., 2006). When latrunculin was microinjected into the NAcore, it reduced spine density and caused a corresponding decrease in F-actin and PSD-95 in the postsynaptic density of cocaine-withdrawn but not drug-naïve animals. Latrunculin also abolished the increase in NAcore head diameter and behavioral sensitization (as measured via locomotor activity). Surprisingly, latrunculin microinjection into the NAcore potentiated cocaine-induced reinstatement, indicating that the increase in F-actin after cocaine withdrawal may be compensatory relative to drug-seeking behavior (Toda et al., 2006, 2010). In a similar line of research, others found that inhibition of actin cycling in the amygdala selectively disrupted methamphetamine-associated memory in methamphetamine CPP and contextual renewal of methamphetamine seeking (Young et al., 2014).

Recent technologies allow us to determine cell-type specificity of spine morphology, most often using BAC transgenic mice that selectively label D1- or D2-expressing MSNs and viral vectors that selectively target these cell subpopulations. A majority of studies show that cocaine-induced structural plasticity and synaptic plasticity alterations in the NAc are preferentially observed in or are more persistent in D1 MSNs (Golden and Russo, 2012). With prolonged, repeated noncontingent cocaine treatment, there is a selective increase in dendritic spine density in D1 MSNs in the NAc (core and shell) with an increase in spine diameter in the NAcore during early but not late withdrawal (Dobi et al., 2011). These results were indirectly corroborated by a study showing that D1 receptor knockout mice fail to display cocaine-induced morphologic changes; D1 receptor but not D2 receptor antagonists likewise prevented the increase in spine density, although the cell-type specificity of these changes was not investigated (Ren et al., 2010). In contrast, others have reported that repeated cocaine treatment increases dendritic spine density in both cell types (Lee et al., 2006; Li et al., 2012), although these changes still only persist in D1 MSNs (Lee et al., 2006). Inconsistencies between the various reports of noncontingent cocaine delivery may be attributed to a variety of factors, including drug dose, withdrawal time, and analysis method. A number of reports indicate that cocaine-induced behaviors, including seeking and sensitization, are mediated by activation of D1 MSNs (Ferguson et al., 2011; Lobo and Nestler, 2011; Bock et al., 2013; Smith et al., 2013). Pertinent to mechanism, cotransducing the NAshell of the BAC transgenic mice with the Cre-dependent herpes simplex virus (HSV)–mCherry and HSV–green fluorescent protein–ΔFosB allowed for analysis of spine morphology alterations by ΔFosB. Acute drug exposure (including most drugs of abuse) has been shown to induce the long-lasting accumulation of ΔFosB in the NAc (Nestler, 2008), and noncontingent cocaine-induced alterations in spine morphology have been shown to be dependent on ΔFosB (Maze et al., 2010). Using transgenic mice, ΔFosB was found to selectively increase dendritic spine density in D1- but not D2-expressing MSNs after repeated injections of noncontingent cocaine (Grueter et al., 2013). The cell-type specificity of the other molecular mechanisms underlying drug-induced plasticity summarized above is yet to be investigated.

VI. Pharmacological Inhibition of Drug Seeking

Paleontological and archeological studies estimate that for more than 10,000 years, humans have used pharmacological agents such as alcohol and medicinal plants to induce altered states (Sullivan and Hagen, 2002; Saah, 2005). Historically, the imbibing of intoxicating materials commonly took place to facilitate performance of religious rites, treat pain, and simply to seek pleasure. As such, medicinal strategies designed to treat the unpleasant side effects of chronic exposure to alcohol and other euphoria-inducing substances began at least 1900 years ago, when the Egyptians, under Greco-Roman rule, describe a medicinal approach to treating alcohol hangovers (Hirt et al., 2014). The study and use of pharmacological agents to inhibit drug seeking has rapidly developed surrounding the relatively recent shift in our understanding that addiction per se is not a moral dilemma, but rather a disease of unmanageable motivation (Kalivas et al., 2005). In this light, regulating plasticity in the NAc, which is crucial for goal-directed and motivated behaviors (Berridge and Robinson, 1998), through the control of glutamatergic signaling is an effective way to inhibit drug seeking to the majority of drugs of abuse (Kalivas, 2009; Scofield and Kalivas, 2014). This section on the

pharmacological modulation of glutamate systems in the NAc as a means for inhibiting drug seeking is organized based on drug ligand receptors, followed by the pharmacological agents that target these receptors and their effects on multiple types of drug-seeking behavior.

A. α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid Receptors

As discussed above, in the accumbens, activation of AMPARs is required for the acute excitation of MSNs by glutamatergic inputs that are required to induce drug seeking (Wolf and Ferrario, 2010). Systemic delivery of AMPAR antagonists inhibits cue-induced cocaine (Bäckström and Hyytiä, 2003) and ethanol (Bäckström and Hyytiä, 2004) seeking, as well as methamphetamine (Miyatake et al., 2005) and amphetamine (Mead and Stephens, 1999) CPP and the induction and expression of amphetamine behavioral sensitization (Karler et al., 1991). Evidence suggests that the efficacy of the systemic delivery of AMPA antagonists is enacted at least in part by glutamatergic neurotransmission in the accumbens, because systemic administration of the AMPAR antagonist 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[*f*]quinoxaline-2,3-dion (NBQX) inhibited cue-induced reinstatement of cocaine seeking and was accompanied by decreased activity in NAcore neurons (Zavala et al., 2008).

Infusion into the NAc of the glutamate analog AMPA (which serves as a selective AMPAR agonist) alone initiates cocaine seeking to levels that parallel reinstated drug seeking precipitated by a noncontingent injection of cocaine (Ping et al., 2008). In these experiments, AMPA infusion into the NAshell was more effective at producing cocaine-seeking behavior than infusions made into the NAcore, yet both produced a significant effect (Ping et al., 2008). The importance of AMPARs in cocaine seeking is further illustrated by downregulating the AMPAR subunit GluR1 mRNA in the accumbens using an oligonucleotide antisense strategy to decrease both cocaine- and AMPA-primed reinstatement of cocaine seeking. This effect is also observed when inhibitory nucleic acid is delivered to either the NAcore or NAshell (Ping et al., 2008).

Cocaine seeking can be induced through the microinfusion of cocaine into the mPFC, and this behavior is blocked by infusion of the AMPAR antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) into the accumbens (no distinction between NAcore and NAshell) (Park et al., 2002). When CNQX is delivered directly to the NAcore, the motor stimulant effect of a cocaine injection in cocaine-sensitized animals is inhibited (Pierce et al., 1996), as is responding during cocaine self-administration (Cornish et al., 1999; Suto et al., 2009) and intake during extended access to cocaine (Doyle et al., 2014). Furthermore, infusion of CNQX into the NAcore reduces cue-induced (Bäckström and Hyytiä, 2007), context-induced (Xie et al., 2012), and cocaine-primed (Cornish and Kalivas, 2000; Famous et al., 2008) reinstatement of cocaine seeking. AMPAR blockade–mediated inhibition of cocaine seeking disrupts the efficacy of a conditioned cue to engage cocaine seeking, because delivery of the AMPAR antagonist LY293558 [(3*S*,4a*R*,6*R*,8a*R*)-6-[2-(1*H*-tetrazol-5-yl)-ethyl]decahydroisoquinoline-3-carboxylic acid] into the NAcore decreases active lever responding, yet increases inactive lever responding (Di Ciano and Everitt, 2001). Infusion of CNQX into the NAcore also inhibits both cue-induced and drug-primed heroin seeking (LaLumiere and Kalivas, 2008). However, infusion of CNQX into the accumbens (no distinction made between the NAcore and NAshell) attenuates the locomotor response to a D-amphetamine administration in animals conditioned by previous D-amphetamine exposure (Burns et al., 1994).

As discussed above, accumbens MSNs express increased levels of CP-AMPARs after the incubation of cocaine craving. Interestingly, NAc infusion of Naspm, a selective antagonist of GluR2-lacking CP-AMPARs, inhibits cued cocaine seeking, demonstrating the importance of this drug-induced alteration of the AMPAR subunit expression profile (Conrad et al., 2008). Moreover, cocaine-induced reinstatement of lever pressing is associated with a transient increase in AMPARs and this is prevented by pretreatment into the NAcore or NAshell with a cell-permeable peptide (Pep2-EVKI) that disrupts GluR2 trafficking to the membrane (Famous et al., 2008).

B. N-Methyl-D-Aspartate Receptors

As discussed above, NMDARs serve as key regulators of the synaptic plasticity linked to the neurologic processes controlling learning and memory (Morris, 2013), with pharmacological blockade of NMDARs being a common mechanism of action for dissociative anesthetic drugs including ketamine and dizoclipine (Mion and Villevieille, 2013). Systemic administration of the noncompetitive NMDAR antagonist dizoclipine (MK-801 or [5*R*,10*S*]-[+]-5-methyl-10,11- dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine) disrupts the reconsolidation of cocaine context-associated memory prior to testing for a CPP (Brown et al., 2008), yet it has no effect on cocaine-primed reinstatement. However, when cocaine is not on board, systemic administration of MK-801 dose-dependently reinstates cocaine seeking in extinguished animals (De Vries et al., 1998). Systemic delivery of MK-801 also inhibits nicotine-induced sensitization of locomotor activity (Shoaib and Stolerman, 1992) and amphetamine CPP (Table 2) (Tzschentke, 2007). However, MK-801 is possibly reinforcing, because studies show that MK-801 produces a CPP when given alone to naïve mice (Panos et al., 1999). Furthermore, animals will directly self-administer MK-801 microinfusions into the NAshell, but not the NAcore (Carlezon and Wise, 1996).

Another pharmacological agent that inhibits NMDAR signaling (although it has also been shown to activate $GABA_A$ receptor signaling; Williams, 2005) is *N*-acetyl homotaurine (acamprosate), which is used to treat alcohol withdrawal in humans (Franck and Jayaram-Lindström, 2013). In preclinical studies, systemic administration of acamprosate inhibits cue-induced and drug-primed cocaine seeking (Bowers et al., 2007), cue-induced nicotine seeking (Pechnick et al., 2011), as well as cocaine and ethanol CPP (McGeehan and Olive, 2003a) and the reinstatement of cocaine CPP (McGeehan and Olive, 2006). Interestingly, acamprosate inhibits morphine-induced sensitization (but does not inhibit stress or drug-primed reinstatement of heroin seeking), an effect that is accompanied by reduced dopamine levels in the NAshell (Spanagel et al., 1998). Similar results are obtained in ethanol studies in which acamprosate inhibits ethanol intake and CPP, which is also associated with reduced levels of dopamine release in the NAshell (Olive et al., 2002). Studies performed in neocortical cultures suggest that acamprosate treatment exerts its therapeutic effect, at least in part, through preventing glutamate excitotoxicity during ethanol withdrawal (al Qatari et al., 2001)

Yet another pharmacological agent that inhibits activation of NMDARs is memantine, which is commonly used in the treatment of Alzheimer's disease as a means of inhibiting neuronal excitotoxicity (Zádori et al., 2014). When given systemically, memantine inhibits morphine (Ribeiro Do Couto et al., 2004) and cocaine (Kotlińska and Biała, 2000) CPP, as well as nicotine but not cocaine self-administration (Blokhina et al., 2005). Studies show that memantine treatment also reverses cocaine-induced reductions in the expression of tumor necrosis factor-α in the NAc of animals that show inhibited cocaine CPP (no distinction made between the NAcore and NAshell) (Lin et al., 2011).

Accumbens NMDAR-dependent plasticity is required for the early stages of learning. Accordingly, studies show that blockade of accumbens NMDARs inhibits the acquisition of an operant sucrose self-administration task, yet it has no effect on lever pressing for sucrose once the task is learned (Kelley et al., 1997). Studies show that infusion of (2*R*)-amino-5-phosphonovaleric acid (AP5) into the NAcore dose-dependently inhibits cocaine-induced locomotion, whereas infusion of AP5 into the NAshell has no effect. However, the same group also reports that infusion of AP5 into the NAshell produces an increase in spontaneous locomotion, whereas infusion into the NAcore has no effect on activity (Pulvirenti et al., 1994). Infusion of AP5 in the NAcore or NAshell also enhances context-induced, cocaine-conditioned locomotion (Rodríguez-Borrero et al., 2006). Interestingly, contradictory evidence for the role of AP5 infusion on reinstated cocaine seeking exists, with one report demonstrating that AP5 infusion into the NAcore or NAshell induces reinstated cocaine seeking, with the NAshell infusion having the stronger effect (Famous et al., 2007), and the other group demonstrating that NMDAR blockade via AP5 infusion into the NAcore dose-dependently inhibits cue-induced cocaine seeking (Bäckström and Hyytiä, 2007). One important consideration is that Famous et al. (2007) used a higher dose of AP5 (3 and 30 μg) to promote reinstated cocaine seeking, whereas Bäckström and Hyytiä (2007) found that lower doses of AP5 (1 and 2 μg) inhibit cue-induced cocaine seeking. Infusion of AP5 into the accumbens (no distinction made between the NAcore and NAshell) also decreases the potentiation of conditioned reinforcement caused by D-amphetamine (Burns et al., 1993) and decreases oral ethanol self-administration (Rassnick et al., 1992).

Systemic administration of the GluN2B-containing NMDAR subtype–specific antagonist ifenprodil inhibits cue- and drug-induced heroin seeking (Shen et al., 2011), cue-induced nicotine seeking (Gipson et al., 2013b), as well as morphine (Suzuki et al., 1999; Ma et al., 2011) and methamphetamine (Miyatake et al., 2005) CPP. Direct infusion of ifenprodil or GluN2B-specific small interfering RNA (siRNA) into the NAcore inhibits cue-induced and drug-primed heroin seeking (Shen et al., 2011). Similarly, infusion of GluN2B-specific siRNA into the NAshell inhibits morphine CPP (Kao et al., 2011), whereas infusion of GluN2B-specific siRNA into the NAcore inhibits cue- and drug-induced heroin seeking (Shen et al., 2011). These data illustrate the importance of the GluN2B-containing NMDAR subtype in mediating accumbens glutamatergic plasticity that underlies opiate reward and drug seeking.

C. Group I Metabotropic Glutamate Receptors (Metabotropic Glutamate Receptors 1 and 5)

Studies show that systemic blockade of postsynaptic Gq-coupled mGluR1 receptors with the antagonist JNJ-16259685 (3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl)-(*cis*-4-methoxycyclohexyl)-methanone) inhibits cocaine behavioral sensitization (Dravolina et al., 2006) as well as cocaine and methamphetamine intake (Achat-Mendes et al., 2012). Furthermore, direct infusion of the same drug (JNJ-16259685) into the NAcore inhibits context-induced cocaine seeking in the drinking-in-the-dark paradigm (Xie et al., 2012), whereas blockade of mGluR1 in the NAshell inhibits ethanol intake in mice.

As described above, extended access cocaine self-administration followed by incubation of craving (approximately 30 days of forced abstinence, without extinction training) dramatically increases drug-seeking behavior and markedly decreases surface expression mGluR1 receptors in the NAc. This incubation-mediated regulation of mGluR1 leads to the accumulation of CP- AMPARs. Using this model, restoration

TABLE 2
Ionotropic GluR pharmacology

Receptor System/Drug	Drug	Action	Delivery	Effect	Reference
AMPA/kainate					
Cocaine	CNQX	Competitive antagonist	Systemic	Inhibited cue-induced reinstatement	Bäckström and Hyytiä, 2003
	NBQX	Antagonist	Systemic	Inhibited cue-induced reinstatement	Zavala et al., 2008
	DNQX	Antagonist	Systemic	Inhibited CPP	Kaddis et al., 1995
	CNQX	Competitive antagonist	NAcore	Inhibited sensitized locomotor response	Pierce et al., 1996
	CNQX	Competitive antagonist	NAcore	Inhibited cocaine intake	Suto et al., 2009
	CNQX	Competitive antagonist	NAcore	Inhibited cocaine intake in extended access	Doyle et al., 2014
	CNQX	Competitive antagonist	NAcore	Inhibited cue-induced reinstatement	Bäckström and Hyytiä, 2007
	CNQX	Competitive antagonist	NAcore	Inhibited context-induced reinstatement	Xie et al., 2012
	CNQX	Competitive antagonist	NAcore	Inhibited drug-primed reinstatement	Cornish and Kalivas 2000
	LY293558	GluR5 AMPA/kainate antagonist	NAcore	Inhibited cue-induced reinstatement	Di Ciano and Everitt, 2001
	AMPA	Agonist	NAshell	Promoted cocaine seeking	Ping et al., 2008
	Naspm	Antagonist of GluA2-lacking AMPA	NAcore / NAshell	Inhibited incubation of cocaine craving	Conrad et al., 2008
Opiates	CNQX	Competitive antagonist	NAcore	Inhibited cue-induced and drug-primed reinstatement	Lalumiere and Kalivas, 2008
Ethanol	CNQX	Competitive antagonist	Systemic	Inhibited cue-induced reinstatement	Bäckström and Hyytiä, 2004
Amphetamines	DNQX	Antagonist	Systemic	Inhibited CPP	Miyatake et al., 2005
	DNQX	Antagonist	Systemic	Inhibited sensitized locomoter response	Karler et al., 1991
	CNQX	Competitive antagonist	Accumbens	Inhibited sensitized locomoter response	Burns et al., 1994
NMDA					
Cocaine	MK-801	Uncompetitive antagonist	Systemic	Inhibited drug-primed CPP	Brown et al., 2008
	MK-801	Uncompetitive antagonist	Systemic	Promoted drug-primed reinstatement	De Vries et al., 1998
	Acamprosate	NMDA antagonist, GABA receptor agonist	Systemic	Inhibited cue-induced and drug-primed reinstatement	Bowers et al., 2007
	Acamprosate	NMDA antagonist, GABA receptor agonist	Systemic	Inhibited CPP	McGeehan and Olive, 2003a
	Acamprosate	NMDA antagonist, GABA receptor agonist	Systemic	Inhibited reinstatement of CPP	McGeehan and Olive, 2006
	Memantine	Antagonist	Systemic	Inhibited CPP	Kotlińska and Biała, 2000
	AP5	Competitive antagonist	NAcore	Inhibited sensitized locomoter response	Pulvirenti et al., 1994
	AP5	Competitive antagonist	NAcore/NAshell	Promoted cocaine-conditioned locomotion	Rodríguez-Borrero et al., 2006
	AP5	Competitive antagonist	NAcore/NAshell	Promoted cocaine seeking	Famous et al., 2007
	AP5	Competitive antagonist	NAcore	Inhibited cue-induced reinstatement	Bäckström and Hyytiä, 2007
Nicotine	MK-801	Uncompetitive antagonist	Systemic	Inhibited sensitized locomoter response	Shoaib and Stolerman, 1992
	Acamprosate	NMDA antagonist, GABA receptor agonist	Systemic	Inhibited cue-induced reinstatement	Pechnick et al., 2011
	Memantine	Antagonist	Systemic	Inhibited intake	Blokhina et al., 2005
Opiates	Acamprosate	NMDA antagonist, GABA receptor agonist	Systemic	Inhibited sensitized locomoter response	Spanagel et al., 1998
	Memantine	Antagonist	Systemic	Inhibited CPP	Ribeiro Do Couto et al., 2004
	Ifenprodil	Antagonist of GluN2B-containing receptors	Systemic	Inhibited cue-induced and drug-primed reinstatement	Shen et al., 2011
	Ifenprodil	Antagonist of GluN2B-containing receptors	Systemic	Inhibited CPP	Suzuki et al., 1999
	Ifenprodil	Antagonist of GluN2B-containing receptors	NAcore	Inhibited cue-induced and drug-primed reinstatement	Shen et al., 2011
Ethanol	Acamprosate	NMDA antagonist, GABA receptor agonist	Systemic	Inhibited CPP	McGeehan and Olive, 2003a
	Acamprosate	NMDA antagonist, GABA receptor agonist	Systemic	Inhibited intake and CPP	Olive et al., 2002
	AP5	Competitive antagonist	Accumbens	Inhibited intake	Rassnick et al., 1992
Amphetamines	MK-801	Uncompetitive antagonist	Systemic	Inhibited CPP	Tzschentke, 2007
	Ifenprodil	Antagonist of GluN2B-containing receptors	Systemic	Inhibited CPP	Miyatake et al., 2005
	AP5	Competitive antagonist	Accumbens	Decreased potentiation of conditioned reinforcement	Burns et al., 1994

of mGluR1 tone with positive allosteric modulators such as Ro67-7476 [(2*S*)-2-(4-fluorophenyl)-1-[(4-methylphenyl)sulfonyl]-pyrrolidine] or SYN119 [9H-Xanthene-9-carboxylic acid (4-trifluoromethyl-oxazol-2-yl)-amide], given either systemically or directly in the NAcore, inhibits cued cocaine seeking (Loweth et al., 2014). Importantly, SYN119 treatment also restored the altered rectification index in electophysiological recordings, indicating that the restoration of mGluR1 tone reverses the accumulation of CP-AMPARs in the accumbens (Loweth et al., 2014).

Like mGluR1, mGluR5 receptors are also Gq coupled and are preferentially localized postsynaptically (Shigemoto et al., 1997). Systemic administration of mGluR5 antagonists inhibits cocaine self-administration (Tessari et al., 2004), CPP (McGeehan and Olive, 2003b), and cue- and drug-induced reinstatement of cocaine seeking (Kumaresan et al., 2009), as well as nicotine self-administration and drug-primed reinstatement (Tessari et al., 2004). Systemic administration of mGluR5 antagonists also inhibits morphine (Popik and Wróbel, 2002) and amphetamine (Herzig et al., 2005) CPP. In addition, systemic administration of fenobam (a mGluR5 negative allosteric modulator) inhibits cue- and drug-induced methamphetamine seeking (Watterson et al., 2013), cocaine intake, and cue- and drug-induced cocaine seeking (Keck et al., 2013). However, like the mGluR2/3 agonist discussed below, both groups found fenobam to reduce sucrose seeking (Keck et al., 2013; Watterson et al., 2013). Additional negative allosteric modulators of mGluR5 are currently under development, including MFZ 10-7 (3-fluoro-5-[2-(6-methyl-2-pyridinyl)ethynyl]benzonitrile hydrochloride), which inhibits cocaine intake as well as cue-induced and drug-primed reinstatement (Keck et al., 2014). Keck et al. report that although 3-((2-methyl-4-thiazolyl)ethynyl)pyridine (MTEP) and MFZ 10-7 lowered rates of sucrose intake, they did not affect overall sucrose intake or locomotor activity.

Studies in animal models of addiction indicate that in the NAcore, the effect of activating postsynaptic Gq-coupled mGluR5 receptors is opposite of that of activating presynaptic mGluR2/3 receptors (Kalivas, 2009; Moussawi and Kalivas, 2010). Infusion of (*S*)-3,5-dihydroxyphenylglycine (group I mGluRs) or 2-chloro-5-hydroxyphenylglycine (specific mGluR5 agonist) into the NAcore promotes the reinstatement of cocaine seeking (Wang et al., 2013; Schmidt et al., 2015), likely via the activation of protein kinase C (Schmidt et al., 2015). (*S*)-3,5-Dihydroxyphenylglycine infusion into the NAshell also promotes cocaine seeking (Schmidt et al., 2015). Infusion of the mGluR5 antagonist MTEP into the NAcore inhibited cue- and drug-induced cocaine seeking (Knackstedt et al., 2014) and cue-induced reinstatement of ethanol seeking (Sinclair et al., 2012). These data suggest that blockade of mGluR5 prevents synaptic potentiation of MSNs in response to glutamate overflow occurring during cue- and drug-primed drug seeking (Fig. 4). Importantly, infusion of MTEP into the NAcore had no effect on cue-induced sucrose seeking (Sinclair et al., 2012), making blockade of postsynaptic mGluR5 a more attractive pharmacological approach for preventing drug seeking than the activation of presynaptic mGluR2/3 receptors (Olive, 2009). Infusion of the mGluR5 antagonist MPEP, directly into the NAshell, also reduces cocaine context-induced locomotion (Martínez-Rivera et al., 2013) as well as cocaine-primed reinstatement of cocaine seeking (Kumaresan et al., 2009). However, it is important to note that although MPEP and MTEP are both mGluR5 antagonists, studies show that MPEP may inhibit NMDARs to a certain extent, whereas MTEP has fewer off-target effects and is more selective for mGluR5 than mGluR1 compared with MPEP (Lea and Faden, 2006).

D. Group II Metabotropic Glutamate Receptors (Metabotropic Glutamate Receptors 2 and 3)

As discussed above, mGluR2/3 receptors are Gi/Go coupled and are normally localized presynaptically (Shigemoto et al., 1997); when activated, these autoreceptors act to limit synaptic release probability. Accordingly, systemic administration of an mGluR2/3-selective agonist such as LY379268 [(1*S*,2*R*,5*R*,6*R*)-2-amino-4-oxabicyclo[3.1.0]hexane-2,6-dicarboxylic acid] inhibits cue- and cocaine-induced cocaine reinstatement (Baptista et al., 2004; Peters and Kalivas, 2006; Cannella et al., 2013), cue- and context-induced nicotine reinstatement (Liechti et al., 2007), cue- and context-induced heroin reinstatement (Bossert et al., 2004, 2005), stress- and cue-induced ethanol reinstatement (Zhao et al., 2006), and cue-induced and drug-primed reinstatement of methamphetamine seeking (Kufahl et al., 2013). When examined, these studies show that systemic LY379268 administration also inhibits cue- and pellet-induced food seeking, although at a higher threshold dose than for inhibiting drug seeking.

In the accumbens, mGluR2/3 is expressed on cortical terminals synapsing on MSNs (Moran et al., 2005). Microdialysis studies show that blockade increases extracellular glutamate levels, whereas activation of mGluR2/3 has the opposite effect, supporting a role for mGluR2/3 autoreceptors in regulating glutamate release at corticoaccumbal synapses (Moussawi and Kalivas, 2010). The tonic activation of mGluR2/3 can be negatively affected by drug-induced alterations in NAcore basal glutamate levels or regulation of receptor function, making activation of this receptor system an attractive candidate for therapeutic intervention. Accordingly, activation of mGluR2/3 receptors in the accumbens proves to be an effective mechanism for inhibiting drug seeking (Table 3) (Olive, 2009). However, it is important to note that mGluR2/3 agonist

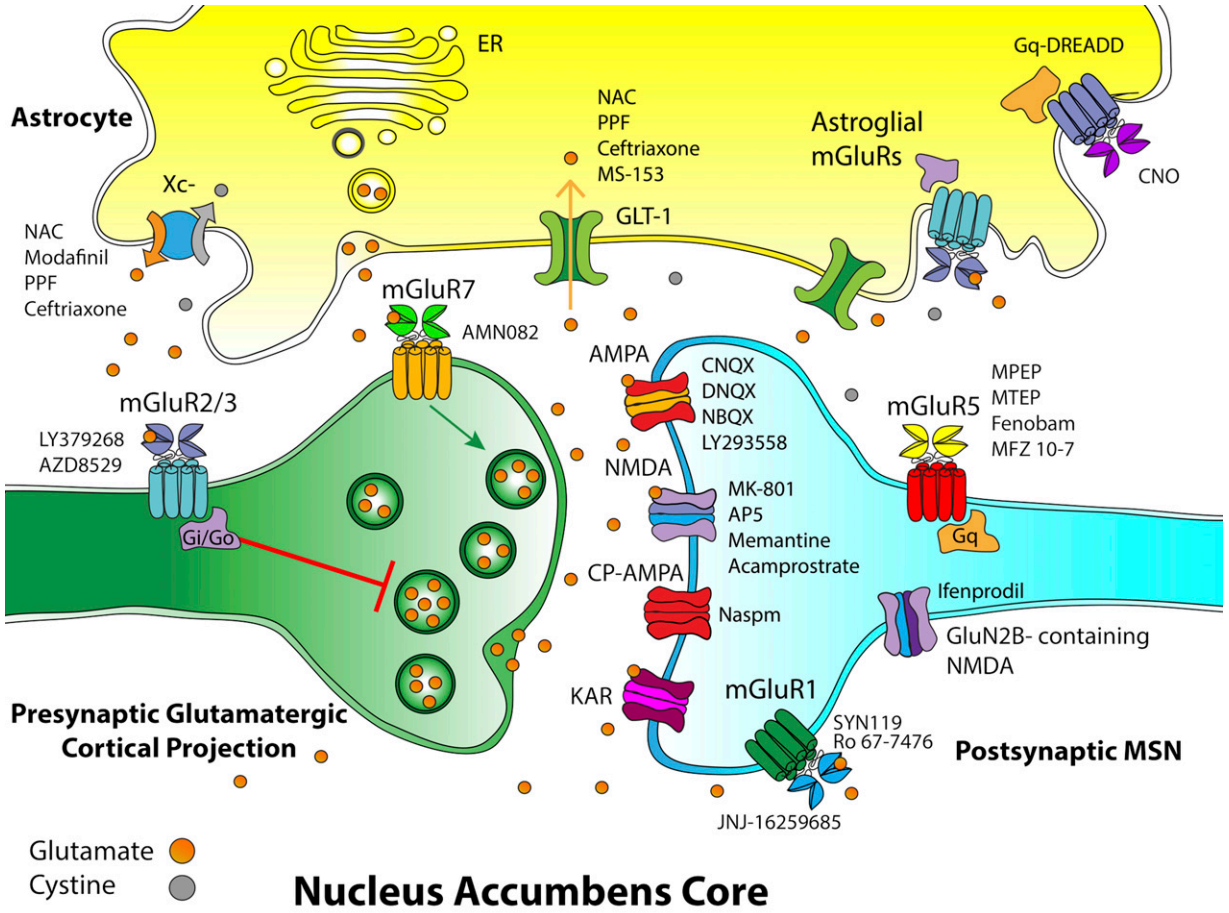

Fig. 4. Pharmacological targets at the glutamatergic NAcore synapse. Shown here is a schematic of a glutamate synapse in the NAcore with the pre- (green) and postsynaptic (blue) terminals as well as an astrocytic contact (yellow). Glutamate is depicted as orange spheres and cysteine is shown as gray spheres. Listed next to AMPA, NMDA, mGLuR2/3, mGluR1, mGluR5, mGluR7, x_c-, and GLT-1 are the drugs that affect these proteins, which have been shown to inhibit drug seeking.

microinjection into the NAcore inhibits locomotion (Besheer et al., 2010) as well as sucrose seeking (Peters and Kalivas, 2006), indicating potential complications for mGluR2/3 agonists as a therapeutic strategy for treating addiction. Direct infusion of LY379268 into the NAcore inhibits cocaine-primed reinstatement (Peters and Kalivas, 2006), cue-induced reinstatement of ethanol seeking (Besheer et al., 2010; Griffin et al., 2014), cue-induced heroin seeking (Bossert et al., 2005), and hyperlocomotion in rats previously exposed to amphetamine (Chi et al., 2006). Furthermore, systemic administration of LY379268 inhibits increased dopamine in the NAshell elicited by nicotine administration in a nicotine-paired context (D'Souza et al., 2011), supporting a possible role for hetero-mGluR2/3 receptors that presynaptically regulate dopamine release (Baker et al., 2002). In addition, infusion of LY379268 directly into the NAshell reduced cue-induced nicotine seeking (Liechti et al., 2007), as well as context-induced heroin seeking (Bossert et al., 2006).

An emerging compound showing promise in treating addiction to multiple classes of addictive substances is trifluoromethoxy)phenyl]methyl]-3H-isoindol-1-one (AZD8529), an mGluR2-specific positive allosteric modulator. Systemic administration of this compound decreases cued nicotine intake and cue- and nicotine-induced seeking (Justinova et al., 2015) as well as cue-induced methamphetamine seeking (Caprioli et al., 2015). Interestingly, AZD8529 was effective at inhibiting cued nicotine seeking at doses that did not affect food seeking, indicating that the selective activation of mGluR2 may prove a more effective treatment of relapse given the lack of a negative effect on natural rewards.

E. Group III Metabotropic Glutamate Receptors (Metabotropic Glutamate Receptor 7)

Similar to mGluR2/3 receptors, mGluR7 receptors are presynaptically localized (Li and Markou, 2015). However, in contrast with mGluR2/3 stimulation, mGluR7 activation augments glutamate and GABA release (Li et al., 2013). Systemic administration of AMN082 (*N*,*N*′-dibenzhydrylethane-1,2-diamine dihydrochloride), a selective mGluR7 agonist, inhibits cocaine intake and cocaine- and heroin-primed reinstatement (Li et al., 2010), as well as ethanol intake and ethanol-primed CPP (Salling et al., 2008; Bahi et al., 2012). Interestingly, microinjection of the mGluR7 agonist AMN082 in

TABLE 3
mGluR pharmacology

	Drug	Action	Delivery	Effect	Reference
Group I (mGluR1/5)					
Cocaine	JNJ-16259685	mGluR1 NAM	Systemic	Inhibited sensitized locomoter response	Dravolina et al., 2006
	JNJ-16259685	mGluR1 NAM	Systemic	Inhibited intake	Achat-Mendes et al., 2012
	MPEP and MTEP	mGluR5 NAM	Systemic	Inhibited cue-induced and drug-primed reinstatement	Kumaresan et al., 2009
	Fenobam	mGluR5 NAM	Systemic	Inhibited intake, cue-induced and drug-primed reinstatement	Keck et al., 2013
	MFZ 10-7	mGluR5 antagonist	Systemic	Inhibited intake, cue-induced and drug-primed reinstatement	Keck et al., 2014
	MPEP	mGluR5 NAM	Systemic	Inhibited intake	Tessari et al., 2004
	MPEP	mGluR5 NAM	Systemic	Inhibited CPP	McGeehan and Olive, 2003b
	SYN119	mGluR1 PAM	NAcore	Inhibited incubation of cocaine craving	Loweth et al., 2014
	Ro67-7476	mGluR1 PAM	NAcore	Inhibited incubation of cocaine craving	Loweth et al., 2014
	JNJ-16259685	mGluR1 NAM	NAcore	Inhibited context-primed reinstatement	Xie et al., 2012
	MTEP	mGluR5 NAM	NAcore	Inhibited cue-induced and context-primed reinstatement	Knacksted et al., 2013
	MPEP	mGluR5 NAM	NAshell	Inhibited cocaine context-induced locomotion	Martínez-Rivera et al., 2013
	MPEP	mGluR5 NAM	NAshell	Inhibited drug-primed reinstatement	Kumaresan et al., 2009
	CHPG	mGluR5 agonist	NAcore	Promoted cocaine-seeking cue-induced reinstatement	Wang et al., 2013
	DHPG	mGluR1/5 agonist	NAcore	Promoted cocaine seeking	Schmidt et al., 2015
	DHPG	mGluR1/5 agonist	NAshell	Promoted cocaine seeking	Schmidt et al., 2013
	DHPG	mGluR1/5 agonist	NAcore	Inhibited cocaine seeking after incubation	Loweth et al., 2014
Nicotine	MPEP	mGluR5 NAM	Systemic	Inhibited intake and drug-primed reinstatement	Tessari et al., 2004
Opiates	MPEP	mGluR5 NAM	Systemic	Inhibited CPP	Popik and Wróbel, 2002
Ethanol	JNJ-16259685	mGluR1 NAM	NAshell	Inhibited intake	Lum et al., 2014
	MTEP	mGluR5 NAM	NAcore	Inhibited cue-induced reinstatement	Sinclair et al., 2012
Amphetamines	JNJ-16259685	mGluR1 NAM	Systemic	Inhibited intake	Achat-Mendes et al., 2012
	Fenobam	mGluR5 NAM	Systemic	Inhibited cue-induced and drug-primed reinstatement	Watterson et al., 2013
	MPEP	mGluR5 NAM	Systemic	Inhibited CPP	Miyatake et al., 2005
Group II (mGluR2/3)					
Cocaine	LY379268	mGluR2/3 agonist	Systemic	Inhibited cue-induced reinstatement	Cannella et al., 2013
	LY379268	mGluR2/3 agonist	NAcore	Inhibited drug-primed reinstatement	Peters and Kalivas, 2006
Nicotine	LY379268	mGluR2/3 agonist	Systemic	Inhibited cue- and context-induced reinstatement	Liechti et al., 2007
	LY379268	mGluR2/3 agonist	NAshell	Inhibited cue-induced reinstatement	Liechti et al., 2007
	AZD8529	mGluR2 PAM	Systemic	Inhibited intake, cue-induced and drug-primed reinstatement	Justinova et al., 2015
Opiates	LY379268	mGluR2/3 agonist	Systemic	Inhibited cue-induced reinstatement	Bossert et al., 2004, 2005
	LY379268	mGluR2/3 agonist	NAcore	Inhibited cue-induced reinstatement	Bossert et al., 2005
	LY379268	mGluR2/3 agonist	NAshell	Inhibited context-induced reinstatement	Bossert et al., 2006
Ethanol	LY379268	mGluR2/3 agonist	Systemic	Inhibited stress- and cue-induced reinstatement	Zhao et al., 2006
			NAcore	Inhibited intake	Griffin et al., 2014
Amphetamines	LY379268	mGluR2/3 agonist	Systemic	Inhibited cue-induced and drug-primed reinstatement	Kufahl et al., 2013
	LY379268	mGluR2/3 agonist	NAcore	Inhibited sensitized locomotor response	Chi et al., 2006
	AZD8529	mGluR2 PAM	Systemic	Inhibited cue-induced reinstatement	Caprioli et al., 2015
Group III (mGluR7)					
Cocaine	AMN082	Agonist	Systemic	Inhibited intake	Li et al., 2009
	AMN082	Agonist	NAcore/NAshell	Inhibited drug-primed reinstatement	Li et al., 2010
Nicotine	AMN082	Agonist	NAcore/NAshell	Inhibited cue-induced reinstatement	Li and Markou, 2015
Opiates	AMN082	Agonist	Systemic	Inhibited drug-primed reinstatement	Li et al., 2013
Ethanol	AMN082	Agonist	Systemic	Inhibited intake	Salling et al., 2008
	AMN082	Agonist	Systemic	Inhibited drug-primed CPP	Bahi et al., 2012

CHPG, 2-chloro-5-hydroxyphenylglycine; DHPG, (*S*)-3,5-dihydroxyphenylglycine; NAM, negative allosteric modulator; PAM, positive allosteric modulator.

the accumbens increased glutamate levels, whereas it decreased GABA and had no effect on dopamine. The increase in glutamate by AMN082 appears to activate mGluR2/3, since the ability of intra-NAcore infusion of AMN082 to block cocaine-primed reinstatement was blocked with coadministration of an mGluR7 antagonist MMPIP [6-(4-methoxyphenyl)-5-methyl-3-pyridin-4-ylisoxazolo[4,5-*c*]pyridin-4(5*H*)-one] or with the mGluR2/3 antagonist LY341495. Mechanistically, dialysis experiments show that AMN082 blocked cocaine-mediated enhancement of NAcore glutamate in animals after self-administration and extinction, an effect that was reversed by pretreatment with LY341495 (Li et al., 2013). Taken together, these data indicate that the inhibition of drug seeking by activating mGluR7 relies on stimulating mGluR2/3, thereby inhibiting synaptic glutamate release.

F. Glial Glutamate Release and Uptake

Glutamate synaptic transmission in the accumbens is heavily regulated by extrasynaptic glutamate tone provided and maintained by astroglial cells (Scofield and Kalivas, 2014). Given the importance of glutamate transmission in the accumbens with respect to initiating drug-seeking behavior, the mechanisms of glial glutamate release and uptake have been proposed to be particularly relevant in understanding the neurobiology of relapse vulnerability (Kalivas, 2009). Chronic drug exposure alters glutamate synaptic plasticity in the accumbens in part by reducing the expression level of glial proteins that regulate homeostatic levels of extrasynaptic glutamate through glutamate release (via the glial cysteine-glutamate exchanger x_c-) and uptake (via the glia GLT-1) (Scofield and Kalivas, 2014). Drug-induced disruption of these processes affects plasticity by influencing extrasynaptic glutamate levels, leading to the activation or lack of activation of the extrasynaptic mGluRs that influence glutamatergic plasticity (discussed above). Just as pharmacological manipulation of accumbens glutamate receptor systems is an efficient method of manipulating drug-associated behaviors for multiple classes of addictive substances, accumulating evidence indicates that drug-related behaviors in rodents and humans can also be inhibited by regulating the function of these two astroglial processes: glutamate release and uptake (Scofield and Kalivas, 2014).

Ceftriaxone is a cephalosporin β-lactam antibiotic used primarily in the treatment of bacterial meningitis (Knackstedt et al., 2010a). When administered systemically, ceftriaxone enhances GLT-1 and x_c- expression and function in the NAc (Trantham-Davidson et al., 2012; Fischer et al., 2013). The fact that ceftriaxone can reverse drug-induced alterations in synaptic glutamate homeostasis makes it an attractive candidate for the treatment of addiction. Ceftriaxone works best when given repeatedly, and typical treatment regimens range from three to seven uninterrupted sequential doses at 100–200 mg/kg (Scofield and Kalivas, 2014). In animal models of addiction and relapse, ceftriaxone treatment reduces ethanol consumption in alcohol-preferring rats (Sari et al., 2013) and inhibits both cue-induced and cocaine-primed reinstatement (Knackstedt et al., 2010a; Sondheimer and Knackstedt, 2011), as well as cue-induced reinstatement of heroin seeking (Table 4) (Shen et al., 2014b). Studies also show that ceftriaxone inhibits physical dependence and abstinence-induced withdrawal to cocaine amphetamine and methamphetamine using a planaria (flatworm) model system (Rawls et al., 2008). Mechanistically, ceftriaxone-mediated inhibition of drug seeking occurs through normalizing extrasynaptic glutamate levels and by promoting glutamate uptake to countermand drug- or cue-induced glutamate overflow in the NAcore (Kalivas, 2009; Trantham-Davidson et al., 2012). Studies show that ceftriaxone enhancement of the activity and expression of GLT-1 is required for efficacy in inhibiting cued cocaine and heroin seeking (Fischer et al., 2013; Shen et al., 2014b). Perhaps the most promising aspect of ceftriaxone's value as a therapy for addiction is that it provides a long-lasting therapeutic window, allowing protection from cocaine relapse in rodent models when administered weeks before reinstatement (Sondheimer and Knackstedt, 2011). Interestingly, clavulanic acid is a novel structural analog of ceftriaxone that retains the β-lactam core yet has negligible antibiotic activity. Clavulanic acid has greater oral availability and brain penetrability compared with ceftriaxone and enhances expression of GLT-1. Studies show that clavulanic acid treatment inhibits cocaine intake (Kim et al., 2016) as well as morphine CPP (Schroeder et al., 2014). Additional experimentation is required to determine whether clavulanic acid will surpass ceftriaxone as the most effective β-lactam–based treatment of relapse vulnerability.

Modafinil (2-diphenylmethyl-sulfinyl-2 acetamide) is a cognitive-enhancing agent commonly used for treating narcolepsy (Mahler et al., 2014a). Modafinil appears to have a variety of targets and has been reported to modulate dopamine, serotonin, glutamate, norepinephrine, orexin, and histamine systems in the brain (Gerrard and Malcolm, 2007; Mahler et al., 2014a). Because of its ability to increase extracellular dopamine levels, modafinil may serve as replacement therapy for treating psychostimulant addiction; yet paradoxically, modafinil does not induce a robust reinforcing effect in either humans or rodents (Mahler et al., 2014a). Interestingly, systemic administration of modafinil increases extracellular glutamate levels in the NAcore and inhibits cocaine-primed reinstatement. Modafinil's effects appear to occur through activation of x_c-, and subsequent activation of mGluR2/3, because blockade of x_c- or mGluR2/3 in the NAcore inhibits the ability of systemically administered modafinil to block

TABLE 4
Effectors of glial glutamate release/uptake

	Drug	Action	Delivery	Effect	Reference
Cocaine	MS-153	Enhanced GLT-1 function	Systemic	Inhibited CPP	Nakagawa et al., 2005
	Ceftriaxone	Enhanced GLT-1 and xCT	Systemic	Inhibited cue-induced and drug-primed reinstatement	Knackstead et al., 2010
	Clavulanic acid	Enhanced GLT-1	Systemic	Inhibited intake	Kim et al., 2016
	NAC	Enhanced GLT-1, xCT, and glutamate release	Systemic	Inhibited cue-induced and drug-primed reinstatement	Reichel et al., 2011
	PPF	Enhanced GLT-1 and xCT	Systemic	Inhibited cue-induced and drug-primed reinstatement	Reissner et al., 2014
	Glial Gq-DREADD	Enhanced glial Gq signaling	NAcore	Inhibited cue-induced reinstatement	Scofield et al., 2015
Nicotine	Ceftriaxone	Enhanced GLT-1 and xCT	Systemic	Inhibited drug-primed CPP	Alajaji et al., 2013
	NAC	Enhanced GLT-1, xCT, and glutamate release	Systemic	Inhibited cue-induced reinstatement	Ramirez-Niño et al., 2013
Opiates	MS-153	Enhanced GLT-1 function	Systemic	Inhibited CPP	Nakagawa et al., 2005
	Clavulanic acid	Enhanced GLT-1	Systemic	Inhibited CPP	Schroeder et al., 2014
	Ceftriaxone	Enhanced GLT-1 and xCT	Systemic	Inhibited cue-induced reinstatement	Shen et al., 2014b
	NAC	Enhanced GLT-1, xCT, and glutamate release	Systemic	Inhibited cue-induced and drug-primed reinstatement	Zhou and Kalivas, 2008
	Ibudilast	Glial modulator	Systemic	Inhibited CPP	Schwarz and Bilbo, 2013
	PPF	Enhanced GLT-1 and xCT	Systemic	Inhibited CPP	Narita et al., 2006
Ethanol	MS-153	Enhanced GLT-1 function	Systemic	Inhibited intake	Alhaddad et al., 2014
	Ceftriaxone	Enhanced GLT-1 and xCT	Systemic	Inhibited ethanol intake in ethanol-preferring rats	Sari et al., 2013
	Ceftriaxone	Enhanced GLT-1 and xCT	Systemic	Inhibited reinstated ethanol seeking	Qrunfleh et al., 2013
	NAC	Enhanced GLT-1, xCT, and glutamate release	Systemic	Inhibited CPP	Ferreira Seiva et al., 2009
	Ibudilast	Glial modulator	Systemic	Inhibited intake	Bell et al., 2015
	Glial Gq-DREADD	Enhanced glial Gq signaling	NAcore	Inhibited motivation to seek ethanol	Bull et al., 2014
Amphetamines	MS-153	Enhanced GLT-1 function	Systemic	Inhibited CPP	Nakagawa et al., 2005
	Ceftriaxone	Enhanced GLT-1 and xCT	Systemic	Inhibited CPP	Abulseoud et al., 2012
	Ceftriaxone	Enhanced GLT-1 and xCT	Systemic	Inhibited locomoter sensitization	Rasmussen et al., 2011
	NAC	Enhanced GLT-1, xCT, and glutamate release	Systemic	Inhibited cue-induced and drug-primed reinstatement	Unpublished observation
	Modafinil	Enhance extrasynaptic glutamate	Systemic	Inhibited cue, context, and drug-primed reinstatement	Reichel and See, 2010
	Ibudilast	Glial modulator	Systemic	Inhibted intake, locomoter sensitization	Snider et al., 2012/2013
	Ibudilast	Glial modulator	Systemic	Inhibited stress- and cue-induced reinstatement	Beardsley et al., 2010
	Glial Gq-DREADD	Enhanced glial Gq signaling	NAcore	Inhibited cue-induced reinstatement	Scofield et al., 2015

xCT, the catalytic subunit of the cystine-glutamate exchanger.

cocaine-primed reinstatement (Mahler et al., 2014a). Systemic administration of modafinil also inhibits context-induced, cue-induced, and methamphetamine-primed reinstatement of methamphetamine seeking (Reichel and See, 2010). In addition, systemic delivery of modafinil inhibits drug-primed reinstatement of morphine CPP, and this effect is dependent on mGluR2/3 signaling (Tahsili-Fahadan et al., 2010).

NAC is an antioxidant drug and dietary supplement that is a precursor to glutathione and is used in the treatment of acetaminophen poisoning (Murray et al., 2012b). NAC has diverse effects, including antioxidant activity, inhibition of inflammatory cytokine release, and modulation of dopamine release. Importantly, because NAC is a cystine prodrug, it also serves as a substrate for cystine-glutamate exchange and promotes glial glutamate release via activation of x_c- (Murray et al., 2012b). Moreover, like ceftriaxone, NAC restores expression of GLT-1 and the catalytic subunit of the cystine-glutamate exchanger, xCT, in animals with a history of cocaine exposure (Knackstedt et al., 2010a). Because it promotes glial glutamate release, NAC treatment is an effective means of restoring inhibitory tone on presynaptic mGluRs. Given its ability to upregulate GLT-1, NAC also limits the extent of cue- and drug-induced synaptic glutamate spillflow underlying the reinstatement of drug seeking (Kalivas, 2009). Accordingly, systemic NAC administration reduces cue-induced and drug-primed reinstatement of cocaine (Baker et al., 2003; Murray et al., 2012a; Ducret et al., 2015), heroin (Zhou and Kalivas, 2008), and nicotine seeking (Ramirez-Niño et al., 2013) and also inhibits ethanol CPP (Ferreira Seiva et al., 2009). Physiological analyses reveal that cocaine- and heroin-induced loss of LTD and LTP induced in the NAcore after in vivo electrical stimulation of the PFC is reversed by daily NAC treatment (Moussawi et al., 2011; Shen and Kalivas, 2013). Interestingly, the ability

of NAC to restore plasticity at PFC synapses in the NAcore requires signaling through mGluR2/3 (Moussawi et al., 2009). Like ceftriaxone and reinstated heroin seeking discussed above, restoration of GLT-1 expression by NAC in the NAcore is required for inhibiting both cue and cocaine-primed reinstatement (Reissner et al., 2015). Another advantage of NAC as a therapy for addiction is robust efficacy independent of when the drug is administered. NAC treatment is effective in inhibiting drug seeking if given daily during self-administration, injected for 5 days during withdrawal many weeks before a reinstatement trial, or administered acutely just prior to reinstatement trial (Madayag et al., 2007; Reichel et al., 2011; Murray et al., 2012a). In rodent models, NAC treatment also facilitates extinction learning and enhances the rate of extinction of responding for both cocaine and heroin (Moussawi et al., 2011; Murray et al., 2012a). Similar to ceftriaxone, NAC appears to provide extended relapse prevention because daily administration of NAC during abstinence inhibits cocaine seeking up to 14 days after the final NAC injection (Reichel et al., 2011). It should be noted, however, that NAC has not been shown to decrease drug self-administration when administered as drug intake is ongoing, and it also does not inhibit escalation of cocaine self-administration (Ducret et al., 2015).

G. Glial Modulators

Astroctyes are also the target of pharmacological manipulation through the inhibition of other cellular processes including phosphodiesterase (PDE) activity. Ibudilast, commonly used in the treatment of asthma, inhibits PDE activity and possesses anti-inflammatory and neuroprotective effects (Rolan et al., 2009). Systemic administration of ibudilast inhibits ethanol (Bell et al., 2015) and methamphetamine intake (Snider et al., 2013), sensitization of the locomotor response to methamphetamine (Snider et al., 2012), as well as stress- and drug-primed reinstatement of methamphetamine seeking (Beardsley et al., 2010). Ibudilast also reduces morphine withdrawal and CPP, likely as a result of its ability to reduce morphine-induced dopamine release in the NAc (Rolan et al., 2009; Schwarz and Bilbo, 2013). Although ibudilast treatment has a variety of effects that could be beneficial in the pharmacological treatment of addiction, it has yet to be determined whether inhibition of PDE activity, inflammation, or neurotrophic factor release is responsible for its effects on the inhibition of drug-seeking and drug-related behaviors.

The xanthine derivative propentofylline (PPF) inhibits both PDE activity and adenosine uptake (Sweitzer et al., 2001). However, unlike ibudilast, PPF enhances expression of GLT-1 (Tawfik et al., 2006). As such, PPF is an exciting drug that combines the therapeutic action of a glial modulator with the restoration of glutamate homeostasis (discussed in section III), is augmented by exposure to drugs of abuse, and contributes heavily to relapse vulnerability (Kalivas, 2009). As expected, PPF inhibits both cued-induced and drug-primed reinstatement of cocaine seeking (Reissner et al., 2014), as well as morphine CPP (Narita et al., 2006). Interestingly, as is the case for NAC, the ability of PPF to prevent reinstatement required the reversal of cocaine-induced downregulation of GLT-1 expression (Reissner et al., 2014).

As an extension of studies using pharmacological agents that affect astrocytes, astrocyte-specific expression of designer receptors exclusively activated by designer drugs (DREADDs) in the NAcore can be achieved using glial-specific, promoter-driven, adeno-associated viral vectors. Bull et al. (2014) demonstrate that activation of Gq signaling with the hM3D DREADD in NAcore astrocytes enhances internal calcium concentration, facilitates intracranial self-stimulation, and reduces motivation to seek ethanol after 3 weeks of abstinence. Furthermore, activation of astroglial Gq-DREADD promotes glutamate release and inhibits cue-induced cocaine seeking, likely through restoration of glutamate tone on mGluR2/3 receptors in the NAcore similar to what is described above for NAC (Scofield et al., 2015).

In summary, evidence from numerous preclinical models of addiction in rats and mice support the importance of accumbens glutamate transmission in the neurobiological substrates of addiction-related behaviors and the relapse to drug seeking. The vast degree of overlap in these findings likely results from drug-induced glutamatergic dysfunction within the cortico-accumbens circuit, a shared feature of exposure to many types of addictive drugs. Interestingly, these persistent alterations in glutamatergic plasticity are the very molecular basis for the long-lasting relapse vulnerability associated with addiction. Although there is not 100% overlap in the precise molecular alterations caused by each individual drug or in the efficacy of each type of pharmacological manipulation in suppressing addiction-related behaviors, the degree of similarity regarding the efficacy of pharmacological agents discussed above clearly illustrates the value of addiction pharmacotherapies aimed at modulating glutamate synaptic plasticity in treating addictive disorders.

VII. Clinical Outcomes of Targeting Glutamatergic Signaling

This review highlights the importance of glutamate signaling in the NAc as a mechanism of relapse to drug seeking in drug addiction. Glutamate's well established role in drug addiction has prompted clinical trials targeting several proteins implicated in aberrant glutamate signaling. These include ionotropic glutamate receptors such as NMDARs, AMPARs, and mGluRs and glutamate transporters such as GLT-1.

We begin our discussion with NMDAR antagonists. Amantadine (Kornhuber et al., 1994), originally developed as an antiviral medication (Davies et al., 1964), has been the subject of the majority of these trials, with mixed results (Table 5). Small amantadine trials for cocaine dependence have shown positive (Alterman et al., 1992; Kampman et al., 2000), negative (Giannini et al., 1989; Kosten et al., 1992; Robbins et al., 1992; Kampman et al., 2006), or neutral results (in which the active and placebo groups both improved) (Weddington et al., 1991). Memantine, an NMDAR antagonist approved for treatment of late-stage Alzheimer's disease, has demonstrated some potential in treatment of opioid dependence (Bisaga et al., 2001; Krupitsky et al., 2002). However, a small double-blind randomized controlled trial (RCT) demonstrated no effect for treatment of alcohol dependence (Evans et al., 2007). A small trial of the NMDAR antagonist ketamine demonstrated positive effects on laboratory measures of cocaine dependence (Dakwar et al., 2014). This is a provocative finding in light of the fact that ketamine itself has abuse potential (Wolff and Winstock, 2006). Ifenprodil, used clinically in Japan and France as a vasodilator (owing to its action at α-adrenoreceptors), is an NMDAR antagonist selective for GluN2B subunits (Williams, 1993) and is currently being investigated in a clinical trial for adolescent posttraumatic stress disorder. Animal models suggest that ifenprodil might prevent relapse to heroin (Shen et al., 2011) and nicotine (Gipson et al., 2013b), but these results await replication in human clinical trials for drug addiction. Overall, clinical trials of NMDAR antagonists have failed to demonstrate clear efficacy of this class of drugs. This failure may be attributable to issues around timing of administration. For example, MK-801 administered during repeated noncontingent cocaine injections prevents locomotor sensitization (MacAskill et al., 2014) but can induce reinstatement of cocaine seeking if administered after extinction training (De Vries et al., 1998).

Another well studied NMDAR-targeting approach involves the NMDAR coagonist D-cycloserine (Watson et al., 1990), which enhances extinction learning in preclinical models of addiction (Myers et al., 2011). This finding has led to several small clinical trials for its use in augmenting cue-exposure therapies for addiction, again with mixed results. These are primarily small proof-of-concept trials with a primary outcome of "cue reactivity." Cue reactivity encompasses objective measures of sympathetic arousal and/or subjective reports of craving, induced by paraphernalia or pictures associated with the abused drug. These small proof-of-concept trials have shown decreased cue reactivity for nicotine (Santa Ana et al., 2009), no effect compared with placebo for nicotine (Kamboj et al., 2012; Yoon et al., 2013) and alcohol (Kamboj et al., 2011; Watson et al., 2011), or increased cue reactivity for cocaine (Price et al., 2009, 2013) and alcohol (Hofmann et al., 2012). One study that investigated clinically meaningful outcomes of D-cycloserine for augmenting cue-exposure therapy found negative results for nicotine use (Yoon et al., 2013).

Acamprosate (the calcium salt of *N*-acetylhomotaurinate) is included in this section because of its hypothesized action on NMDARs, where it has been reported to have both agonist (Madamba et al., 1996) and antagonist (Rammes et al., 2001) effects. However, a recent study suggests that it is the calcium salt, rather than the purported NMDAR ligand *N*-acetylhomotaurinate, that ameliorates alcoholic behavior in both preclinical and clinical applications (Spanagel et al., 2014). Acamprosate is the subject of more clinical research than any other compound in this section, and meta-analyses suggest that it is effective in the treatment of alcoholism (Dranitsaris et al., 2009; Mason and Lehert, 2012; Jonas et al., 2014). Limited clinical research suggests that it is not effective in treating cocaine addiction (Kampman et al., 2011).

AMPARs and kainate receptors represent the other main classes of ionotropic glutamate receptors. To date, no clinical trials have investigated drugs specifically targeting these receptors for the treatment of addiction. However, these receptors are among the many putative targets of topiramate (Follett et al., 2004). Topiramate is likely the most efficacious drug reviewed here for treating cocaine addiction (Johnson et al., 2013) and it is also effective in treating alcohol addiction (Baltieri et al., 2008; Rubio et al., 2009), although it shows limited efficacy in treating comorbid alcohol and cocaine addiction (Kampman et al., 2013). Topiramate is efficacious for treating smoking addiction in men, but not women (Anthenelli et al., 2008). It has very limited efficacy in treating methamphetamine addiction (Elkashef et al., 2012; Ma et al., 2013). Thus, although the mechanism by which topiramate treats substance use disorders is not entirely clear, it appears to be one of the better clinical tools available for treating addiction.

Another drug in this vein is modafinil. Modafinil's best-characterized cellular target is the dopamine transporter (Volkow et al., 2009), but it modulates the actions of multiple neurotransmitter systems (Ferraro et al., 1998; Ishizuka et al., 2010). Although modafinil is officially indicated only for the treatment of excessive daytime sleepiness, there is preclinical evidence to suggest that it may be used clinically for the treatment of substance use disorders. Importantly, for the purposes of this review, it appears that modafinil's efficacy against substance use disorders depends on glutamatergic signaling (Tahsili-Fahadan et al., 2010; Mahler et al., 2014b).

Three double-blind, placebo-controlled trials have investigated modafinil as a treatment of cocaine use disorder with ambiguous demonstration of efficacy. One group demonstrated efficacy in a small early trial

TABLE 5
Clinical trials

Medication	Patient Population	Study Design	No. of Patients	Results	Reference
Amantadine	Cocaine use disorder	Double-blind RCT	42	Decreased positive urine	Alterman et al., 1992
	Cocaine use disorder	Double-blind RCT	199	No increase in cocaine abstinence due to amantadine	Kampman et al., 2006
	Cocaine use disorder	Double-blind RCT	30	No more effective than placebo in combatting withdrawal symptoms	Giannini et al., 1989
	Cocaine use disorder	Double-blind RCT	61	Fewer positive urines, decreased cocaine use	Kampman et al., 2000
	Cocaine use disorder	Single blind RCT	94	No difference in positive urine	Kosten et al., 1992
	Cocaine use disorder	Double-blind RCT	54	No difference in positive urine	Weddington et al., 1991
Memantine	Opiate use disorder	Laboratory trial	8	Decreased self-reported withdrawal precipitated by naloxone	Bisaga et al., 2001
	Opiate use disorder	Single blind RCT	67	Decreased self-reported heroin craving	Krupitsky et al., 2002
	Alcohol use disorder	Double-blind RCT	27	Placebo group showed larger decrease in drinking	Evans et al., 2007
Ketamine	Cocaine use disorder	Laboratory trial	8	Decreased self-reported craving	Dakwar et al., 2014
D-Cycloserine	Tobacco use disorder	Laboratory trial	25	Decreased carbon monoxide at follow-up but no overall change in smoking behavior	Santa Ana et al., 2009
	Tobacco use disorder	Laboratory trial	32	No change in cue reactivity, slight reduction in self-reported craving	Kamboj et al., 2012
	Tobacco use disorder	Double-blind RCT	29	No decrease in cigarette smoking (participants were not seeking treatment of cocaine)	Yoon et al., 2013
	Heavy drinkers	Laboratory trial	36	No change in cue reactivity	Kamboj et al., 2011
	Alcohol use disorder	Laboratory trial	16	No change in self-reported craving	Watson et al., 2011
	Cocaine use disorder	Laboratory trial	32	No change in self-reported craving or cocaine use	Price et al., 2013
	Cocaine use disorder	Laboratory trial	10	Trend toward increased craving due to treatment	Price et al., 2009
	"Problem drinkers"	Laboratory trial	20	Transient increase in craving	Hofmann et al., 2012
Acamprosate	Cocaine use disorder	Double-blind RCT	60	No decrease in cocaine use	Kampman et al., 2011
Topiramate	Cocaine use disorder	Double-blind RCT	142	Decrease in cocaine-positive urine	Johnson et al., 2013
	Alcohol use disorder	Double-blind RCT	155	Decreased drinking for topiramate	Baltieri et al., 2008
	Alcohol use disorder	Double-blind RCT	63	Decreased drinking	Rubio et al., 2009
	Tobacco use disorder	Double-blind RCT	87	Decreased smoking for men only	Anthenelli et al., 2008
	Methamphetamine use disorder	Double-blind RCT	140	Decreased "relapse" (positive urine collected 6–12 weeks from baseline-abstinent participants)	Elkashef et al., 2012; Dackis et al., 2005
Modafinil	Cocaine use disorder	Double-blind RCT	210	No differences overall; trend toward increased abstinence only among male patients	Dackis et al., 2012
	Cocaine use disorder	Double-blind RCT	210	No differences overall; decreased craving, increased consecutive nonuse	Anderson et al., 2009
	Methamphetamine use disorder	Double-blind RCT	210	No differences overall; increased abstinence among most compliant patients	Anderson et al., 2012
	Methamphetamine use disorder	Double-blind RCT	71	No differences overall; trend toward efficacy in high baseline use and CBT nonattendance	Heinzerling et al., 2010
	Methamphetamine use disorder	Double-blind RCT	80	No differences overall; trend toward efficacy in medication-compliant subjects	Shearer et al., 2009
	Tobacco use disorder	Double-blind RCT	157	Trial discontinued due to increased smoking and withdrawal symptoms	Schnoll et al., 2008
NAC	Cannabis use disorder (adolescents)	Double-blind RCT	116	Increased negative cannabis-positive urine	Gray et al., 2012
	Cocaine use disorder	Double-blind RCT	111	No change in cocaine-positive urine; increased time to relapse in baseline abstinent participants	LaRowe et al., 2013
	Cocaine use disorder	Laboratory trial	15	NAC decreases self-reports of craving and interest in response to images of cocaine	LaRowe et al., 2007
	Cocaine use disorder	Laboratory trial	6	NAC decreases craving after experimentally administered cocaine	Amen et al., 2011
	Methamphetamine use disorder	Double-blind RCT	31	Combination treatment does not affect objective or subject measures of methamphetamine use disorder	Grant et al., 2010
	Tobacco use disorder	Open label	19	Combination treatment reduces cigarettes smoked per day with minimal side effects	McClure et al., 2014a,b
	Tobacco use disorder	Laboratory trial	22	NAC decreases subjective reward after experimentally delivered cigarette	Schmaal et al., 2011
	Tobacco use disorder	Double-blind RCT	29	Decrease in self-reported cigarettes after excluding two heavy drinkers	Knackstedt et al., 2009
	Tobacco use disorder	Double-blind RCT	28	NAC briefly decreases self-reported smoking and decreases gambling	Grant et al., 2014

CBT, cognitive-behavioral therapy.

(Dackis et al., 2005) that failed to replicate in a later trial (Dackis et al., 2012), although the later trial demonstrated a trend toward efficacy among male patients (approximately 70% of participants included in the original trial were men). A third trial (Anderson et al., 2009) demonstrated no overall efficacy in the primary outcome measure (total percentage of nonuse days) but post hoc analyses revealed an increased number of consecutive nonuse days, reduced craving, and an increased percentage of nonuse days among patients without a history of alcohol use disorder.

Three double-blind, placebo-controlled trials have investigated modafinil as a treatment of methamphetamine use disorder. None showed clear efficacy for this indication. However, two of these studies (Shearer et al., 2009; Anderson et al., 2012) indicate through post hoc analyses that patients compliant with the medication do achieve better abstinence than noncompliant patients. Another study (Heinzerling et al., 2010) showed trends toward increased efficacy among users with high baseline methamphetamine use and low attendance in cognitive-behavioral therapy (although neither was statistically significant).

Interestingly, the one trial conducted to date on treatment of tobacco use disorder (Schnoll et al., 2008) indicates that modafinil is harmful for treating these patients, both in terms of smoking behavior and withdrawal symptoms. This trial was halted as a result.

Thus, modafinil seems moderately efficacious at best in treating substance use disorders. Its efficacy may be obscured by the high rates of noncompliance (which in turn may result from the fact that it blunts the euphoric effects of drug use, at least in the case of cocaine; Dackis et al., 2003). Gender differences may account for some of the lack of efficacy, at least in the case of cocaine. More concerning are the interactions of modafinil treatment with tobacco and alcohol use disorder. Tobacco use disorder is directly exacerbated by modafinil, and alcohol use disorder prevents modafinil from effectively treating cocaine use disorder. The high rates of comorbid substance use disorders with alcohol and tobacco use disorders likely will prevent adoption of modafinil as a first-line clinical treatment, even if future clinical studies can more effectively recruit patients likely to comply with and respond to treatment with modafinil.

mGluRs are the other primary type of glutamate receptor. Reviewed more thoroughly in section V and VI, these receptors are coupled to Gαq or Gαi signaling pathways and can be located on the presynaptic neuron, postsynaptic neuron, or neighboring glia (Pomierny-Chamioło et al., 2014). No clinical trials have yet investigated drugs targeting mGluRs for treating addiction. However, there is preclinical evidence to suggest that fenobam (an mGluR5 negative allosteric modulator) may effectively treat cocaine addiction (Keck et al., 2013), and fenobam has shown promising results in an open-label trial for fragile X (Berry-Kravis et al., 2009). LY404039 [(−)-(1*R*,4*S*,5*S*,6*S*)-4-amino-2-sulfonylbicyclo[3.1.0]hexane-4,6-dicarboxylic acid] is an mGluR2/3 agonist that partly attenuates an animal model of alcohol addiction (Rodd et al., 2006) and has been investigated in a phase 2 trial for schizophrenia (Adams et al., 2013). It remains to be seen whether trials of drugs targeting mGluRs for treating addiction will be successful.

The final molecular target discussed in this section is GLT-1. We recently reviewed the existing clinical trials of GLT-1–modulating agents in the treatment of drug addiction (Roberts-Wolfe and Kalivas, 2015) and summarize key points from that review here. GLT-1 is the primary regulator of extrasynaptic glutamate concentrations in the forebrain. It is downregulated or otherwise dysfunctional in nearly all classes of abused drugs. Small molecules capable of restoring GLT-1 prevent relapse in animal models of drug addiction across drug classes, and this effect depends on restoration of GLT-1 in the NAcore (Fischer et al., 2013; Shen et al., 2014b). There are multiple small molecules capable of restoring GLT-1. However, NAC is the only agent that has been tested in clinical trials to date. NAC is well tolerated, does not have abuse potential, and does not appear to have toxic interaction effects with drugs of abuse. Several clinical trials have investigated NAC as a therapy for drug addiction (Roberts-Wolfe and Kalivas, 2015).

Three laboratory trials have investigated NAC in human patients. NAC reduces craving for cocaine in patients with cocaine use disorder. This holds true regardless of whether craving is induced by experimentally delivering cocaine (Amen et al., 2011) or depicting cocaine-related imagery (LaRowe et al., 2007). However, NAC does not affect the subjective "high" of cocaine or the physiologic response to cocaine-related imagery. In contrast, NAC does decrease the rewarding effects of smoking a first cigarette after a period of abstinence but does not reduce the craving to smoke (Schmaal et al., 2011). Moreover, data from human magnetic resonance spectroscopy studies confirm that as in preclinical studies (Kupchik et al., 2012), NAC normalized levels of extracellular glutamate in the NAcore of cocaine-dependent individuals and, reassuringly, had no effect in control subjects (Schmaal et al., 2012).

One double-blind RCT has investigated NAC for the treatment of cocaine use disorder. This trial found that NAC does not decrease cocaine-positive urine (LaRowe et al., 2013). However, a secondary analysis of these participants demonstrated that NAC significantly delayed time to relapse in a dose-dependent manner. The secondary analysis was low powered, with fewer than 10 subjects each in the placebo, low-dose, and high-dose NAC groups; however, this finding is nonetheless intriguing. Animal models of cocaine use disorder show no evidence that NAC decreases cocaine intake (Ducret

et al., 2015) but consistently demonstrate that NAC reduces relapse. This is consistent with the results of the clinical trial's primary and secondary analyses. A new RCT, recruiting cocaine-dependent individuals who are abstinent at baseline and examining NAC's effects on time to relapse, would likely yield interesting results. Importantly, the treatment strategy of NAC may affect drug use cessation outcomes.

The second high-quality RCT discussed here examined NAC's effects on cannabis use among adolescents (Gray et al., 2012). In contrast with the cocaine trial, NAC decreased cannabis-positive urine in this population. The reasons for NAC's success in this population, in light of the discussion above, are unclear. To our knowledge, almost no basic science research has been conducted on the role of GLT-1 in cannabinoid use, although one study suggests that GLT-1 upregulation may decrease cannabinoid tolerance (Gunduz et al., 2011). A multisite trial investigating the effects of NAC on cannabis use among adults has been launched to follow up on this successful trial in adolescents (McClure et al., 2014a,b).

A few other RCTs have examined NAC for the treatment of methamphetamine (Grant et al., 2010) and tobacco use disorders (Knackstedt et al., 2009; Grant et al., 2014). These trials should be considered as preliminary evidence, because of their small sample sizes and somewhat unusual study design. The clues they offer suggest that NAC may have some utility in treating tobacco use disorder but likely not in treating methamphetamine use disorder. Finally, NAC in combination with varenicline appears to be a promising future strategy, based on the results of a recent open-label trial (McClure et al., 2015).

There are a number of other agents capable of upregulating GLT-1. In the context of substance use disorders, most of the animal model work has investigated small molecules possessing a β-lactam core. Much of this work has been focused on the third-generation cephalosporin ceftriaxone. Concerns about prolonged use of antibiotics and poor central nervous system penetrance have likely discouraged clinical trials investigating ceftriaxone's effects on drug addiction. However, clavulanic acid is a small molecule possessing a β-lactam core that does not suffer from the same concerns as ceftriaxone, and pilot clinical trials of clavulanic acid for drug addiction treatment are underway (ClinicalTrials.gov identifier NCT02563769). Finally, there is low-quality evidence that methylxanthine derivatives may have efficacy in treating drug addiction (Ciraulo et al., 2005)

In summary, a gap remains between basic science demonstrating a role for glutamate signaling in drug addiction and the clinical applications of this basic science. Medications with demonstrated efficacy in the treatment of drug addiction, such as acamprosate and topiramate, may exert their therapeutic effects via glutamate signaling. There is evidence that first-line therapies such as varenicline (Wheelock et al., 2014) and opiate agonist therapies (Verdejo-García et al., 2013) restore glutamate signaling in individuals with nicotine and opiate use disorders, respectively. However, trials of medications targeting glutamate receptors for treating drug addiction have lacked efficacy overall. This may be a result of targeting the wrong glutamate receptor; thus, there is a potential for future trials of small molecules such as ifenprodil (the GluN2B antagonist) and fenobam (the mGluR5 negative allosteric modulator). Early clinical trial failures may alternatively result from a disconnect between the design of clinical trials and animal models of research, as suggested by the RCT with NAC for cocaine use disorder. Depending on the results of future trials specifically testing the role of GLT-1 in relapse (rather than cessation) and the results of the ongoing trial of NAC for cannabis use disorder in adults, GLT-1–restoring therapies may ultimately have a place in clinical treatment of drug addiction. The variety of small molecules with demonstrated ability to upregulate GLT-1 could then be funneled into clinical trials, providing options for clinicians to tailor these therapies to the needs of individual patients based on side effect profiles. In conclusion, there is reason for optimism regarding the future of drug addiction treatment based on strategies targeting glutamate signaling.

VIII. Future Possibilities for Glutamate in Addiction

A. Neurotransmitter Co-Release

Although canonically thought of as purely dopaminergic input, dopamine and glutamate co-release was recently demonstrated in the VTA mesolimbic projection to the NAc (Chuhma et al., 2004; Yamaguchi et al., 2011). Individual fibers from vesicular glutamate transporter (VGlut) 2–positive dopamine neurons form both symmetrical glutamatergic synapses and asymmetric dopaminergic synapses originating from the same axon (Sulzer et al., 1998). Co-release appears to be specific for the mesolimbic pathway, because optogenetic stimulation of VGlut2 neurons evokes robust excitatory postsynaptic potentials in NAc MSNs, but similar excitatory postsynaptic potentials cannot be detected in the dorsal striatum (Stuber et al., 2010). Co-release has an important function in mediating the psychomotor effect of stimulant drugs, because both amphetamine- and cocaine-induced sensitization are significantly reduced by genetic ablation of VGlut2 from dopamine transporter–expressing neurons (Birgner et al., 2010; Hnasko et al., 2010). Interestingly, cocaine CPP is unaffected by this intervention (Hnasko et al., 2010). In contrast with the behavioral effects observed in the sensitization models, dopamine transporter neuron-specific knockout of

VGlut2 increases motivation to obtain sucrose and low doses of cocaine, as well as cue-induced reinstatement of cocaine seeking (Alsiö et al., 2011). These effects can be reconciled by the fact that the specific VGlut2 deletion reduces dopaminergic signaling in the NAc. Glutamate in synaptic vesicles facilitates the packaging of monoamines by increasing the intravesicular pH, which enhances the efficacy of the vesicular monoamine exchanger and leads to increased dopamine concentration per vesicle and enhanced dopamine release (Hnasko et al., 2010).

B. Isolation and Manipulation of the Relapse Engram

Exciting new molecular tools are currently being developed that allow manipulation of neural populations activated during a particular behavior. Early experiments with this technology began as an effort to isolate specific ensembles or groups of neurons responsible for encoding memory traces. Josselyn et al. demonstrated that groups of neurons in the lateral amygdala transiently express enhanced levels of CREB after an auditory fear conditioning (Han et al., 2008; Ploski et al., 2010). These data suggested that the activated neurons could be crucial for the fear memory. This group then used HSV viral vectors to engender CREB-dependent expression of Cre recombinase in combination with Cre-dependent expression of the diphtheria toxin receptor in the lateral amygdala to specifically isolate and destroy this population. Remarkably, after infusion of the diphtheria toxin and the selective death of the CREB-expressing neurons in this region after conditioning, freezing behavior in response to the tone was significantly reduced. Additional experiments performed by Josselyn et al. illustrate that CREB-overexpressing neurons in the lateral amygdala are also important for context-associated cocaine memory using a CPP paradigm, with post-training ablation of this population sufficient to erase the contextual cocaine memory (Hsiang et al., 2014).

Others have employed c-Fos–LacZ transgenic rats in which expression of LacZ is placed under control of the promoter for the IEG c-Fos. Given that expression of c-Fos coincides with neuronal activity, only activated neurons express the LacZ transgene in the c-Fos–LacZ rat model. After the behavior of choice, the Daun02 reagent is infused intracranially into the brain region of choice, resulting in the selective inactivation of the neurons that express LacZ due to β-galactosidase–mediated processing of Daun02 to daunoribicin (Cruz et al., 2013). Similar to the methods described above, neurons activated by a discrete stimulus can be functionally silenced to assess their role in a particular behavior. Interestingly, using this technique, inactivating neurons previously activated by a cocaine-associated context in the NAshell reduced context-mediated reinstatement of cocaine-seeking behavior (Cruz et al., 2014), specifically implicating the NAshell in drug-seeking behavior precipitated by contextual cues.

An extension of this technology functions via transient, inducible expression of Cre recombinase under direction of the promoter of an activity-dependent IEG, like the activity regulated cytoskeletal-associated protein Arc or c-Fos, deemed targeted recombination in active populations (Guenthner et al., 2013; Kawashima et al., 2014). Using this system in combination with the Cre-dependent expression of a gene that allows for control of neuronal activity (e.g., DREADD receptors or channel rhodopsin), ensembles of neurons activated during discreet behavioral tasks can be permanently targeted and manipulated at a later time point. Much like the experiments discussed above, this strategy has produced exciting results. For example, recent work deciphering the role of the cortical amygdala in odor-driven behavior has shown that the after isolation of odor-related ensembles, activation of these neuronal populations in the absence of odor recapitulates responses observed previously during odor exposure (Root et al., 2014). Furthermore, using the same mouse model, deactivating fear-related neural circuits in the hippocampus inhibits freezing behavior after exposure to a fear-inducing context (Denny et al., 2014).

Given that IEG expression can be commensurate with neuronal activity and that IEG expression is observed during reinstated drug seeking in the accumbens (Hearing et al., 2008; Kufahl et al., 2009; Mahler and Aston-Jones, 2012), these new technologies will be particularly useful in decoding and manipulating the ensemble of neurons whose activity is required for initiating drug seeking in both the accumbens and in regions that send projections to the accumbens.

IX. Concluding Comments

In this review, we endeavored to provide the reader with an up-to-date catalog of studies showing that manipulating glutamate transmission in the NAc, with focus on the NAcore, affects animal models of addiction. The preclinical observations relating drug-induced plasticity in glutamatergic synapses further support an important role for glutamate transmission in mediating both the enduring vulnerability to relapse to drug use and how the glutamatergic synapses respond to initiating a relapse event. An important indicator of the potential value of understanding drug-induced glutamatergic plasticity as it relates to addiction is the large number of changes that are shared across multiple classes of addictive drugs, perhaps indicating a common mechanism for shared behavioral symptoms of addiction such as relapse vulnerability. Indeed, we postulate that changes in the capacity of addictive drugs to produce enduring and transient changes in glutamate transmission are shared characteristics of drug relapse, just

as increasing dopamine transmission is a shared characteristic of drug reward and reinforcement. Importantly, clinical studies are beginning to distill the preclinical literature on the role of glutamate synaptic transmission into promising phase I and II trials for treating drug addiction.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Scofield, Heinsbroek, Gipson, Kupchik, Spencer, Smith, Roberts-Wolfe, Kalivas.

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