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The ins and outs of the striatum: Role in drug addiction

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Abstract

Addiction is a chronic relapsing disorder characterized by the loss of control over drug intake, high motivation to obtain drug, and a persistent craving for the drug. Accumulating evidence implicates cellular and molecular alterations within cortico-basal ganglia-thalamic circuitry in the development and persistence of this disease. The striatum is a heterogeneous structure that sits at the interface of this circuit, receiving input from a variety of brain regions (e.g., prefrontal cortex, ventral tegmental area) to guide behavioral output, including motor planning, decision-making, motivation and reward. However, the vast interconnectivity of this circuit has made it difficult to isolate how individual projections and cellular subtypes within this circuit modulate each of the facets of addiction. Here, we review the use of new technologies, including optogenetics and DREADDs (Designer Receptors Exclusively Activated by Designer Drugs), in unraveling the role of the striatum in addiction. In particular, we focus on the role of striatal cell populations (i.e., direct and indirect pathway medium spiny neurons) and striatal dopaminergic and glutamatergic afferents in addiction-related plasticity and behaviors.

Introduction

Drug addiction is a costly and incapacitating disease characterized by uncontrollable drug-taking and drug-seeking, and a high likelihood for relapse, even long after the cessation of drug use. The cortico-basal ganglia-thalamic circuit (Figure 1) has long been known to regulate the development and maintenance of addictive behaviors (Lobo and Nestler, 2011, Luscher and Malenka, 2011, Nestler, 2013, van Huijstee and Mansvelder, 2014). In particular, the striatum, which serves as a central interface of the circuit, has been identified as a key site for the neuroplastic events that underlie addictive processes (Lobo and Nestler, 2011, Luscher and Malenka, 2011, Nestler, 2013, van Huijstee and Mansvelder, 2014). Nonetheless, because of the vast complexity of this circuit, our ability to gain a precise

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understanding of how the specific subcomponents and cell types within areas such as the striatum contribute to addiction has remained elusive. This review will focus on the emergence of new technologies and how they are now allowing us to advance our understanding of the role of striatal afferents and efferents in shaping this chronic, relapsing disease.

Striatal circuitry

The striatum is the major integration site of the cortico-basal ganglia-thalamic circuit, and as such receives a large variety of inputs (Figure 1). In particular, it receives cholinergic inputs from striatal interneurons and brainstem sources (e.g. laterodorsal tegmental area and the pedunclopontine nuclei) and GABAergic inputs from striatal interneurons (Kita, 1993, Dautan et al., 2014). Additionally, it receives dopaminergic inputs from the ventral tegmental area (VTA) and the substantia nigra (SNr) and glutamatergic inputs from several areas, including cortex, hippocampus, amygdala, and thalamus (Swanson, 1982, Phillipson and Griffiths, 1985, Finch, 1996, Groenewegen et al., 1999, Britt et al., 2012). These glutamatergic inputs make contact on the heads of dendritic spines of the striatal GABAergic medium spiny projection neurons (MSNs) whereas dopaminergic inputs synapse onto the spine neck, allowing for an important and complex interaction between these two inputs in modulation of MSN activity (Freund et al., 1984, Xu et al., 1989).

The striatum itself can be divided into two main regions, the dorsal striatum and the nucleus accumbens (NAc), and is comprised of multiple neuronal phenotypes including four different types of interneurons (i.e., cholinergic interneurons and GABAergic interneurons, which express either parvalbumin, calretinin, or nitric oxide synthase/neuropeptide Y/somatostatin) (Kemp and Powell, 1971). However, the majority of striatal neurons (~95%) are MSNs (Kemp and Powell, 1971); these will be the focus of this review. The striatal MSNs in the dorsal striatum can be subdivided into two classes based on their projection patterns, as well as their neuropeptide and receptor expression. MSNs that send monosynaptic projections to the basal ganglia output nuclei (i.e. the SNr and the globus pallidus internal (GPi)) and express dopamine D1 receptors along with the neuropeptides dynorphin and substance P, form part of the direct pathway (dMSNs). MSNs that indirectly project to basal ganglia output nuclei via the globus pallidus external (GPe) and the subthalamic nucleus (STN) and express dopamine D2 receptors and the neuropeptide enkephalin, form part of the indirect pathway (iMSNs) (Gerfen and Surmeier, 2011, Wall et al., 2013). However it should be noted that the MSN projections are not entirely segregated, as some dMSNs send axon collaterals to the GPe/ventral pallidum (VP) (Fujiyama et al., 2011).

Classically, these two striatal MSN populations are thought to have opposing effects on basal ganglia output. Activation of the dMSNs causes a net excitation of the thalamus resulting in a positive cortical feedback loop; thereby acting as a 'go' signal to initiate behavior. Activation of the iMSNs, however, causes a net inhibition of thalamic activity resulting in a negative cortical feedback loop and therefore serves as a 'brake' to inhibit behavior (Gerfen et al., 1982, Albin et al., 1989, Deniau and Chevalier, 1992, Gerfen and Surmeier, 2011, Calabresi et al., 2014). Additionally, basal ganglia output can be influenced

via the hyperdirect pathway, which is a monosynaptic excitatory projection from the cortex to the STN that results in SNr excitation upon activation (Kita et al., 1983). Adding to the complexity of this circuit, the SNr itself projects back to the striatum as well as to the cortex, providing dopaminergic feedback to these structures (Gerfen et al., 1987).

Although these two striatal output pathways also exist in the NAc, the efferent targets of the MSNs are distinct from those in the dorsal striatum and the pathway segregation is much less complete. Specifically, iMSNs in the NAc (i.e., those neurons that express dopamine D2 receptors) project to the VP whereas dMSNs in the NAc (i.e., those neurons that express dopamine D1 receptors) project primarily to the VTA and SNr but also send axon collaterals to the VP (Chang and Kitai, 1985, Lu et al., 1998, Zhou et al., 2003, Tripathi et al., 2010, for review see Smith et al., 2013). It should also be noted that there is a small population of neurons in the NAc that coexpress both D1 and D2 receptors, though this is largely restricted to the NAc shell (Bertran-Gonzalez et al., 2008). For the purpose of providing clarity in this review, we have operationally defined dMSNs as neurons that express dopamine D1 receptors and primarily target the VTA and/or SNr whereas iMSNs are neurons that express dopamine D2 receptors and primarily target the VP or GPe. However, it is important to recognize that depending on the targeting method for a particular manipulation that was performed and the region it was performed in, the distinction between the indirect and direct striatal pathways in a given study may be less than complete.

In addition to the anatomical distinctions described above, the NAc and the dorsal striatum also differ functionally (Haber and McFarland, 1999, Berke and Hyman, 2000, Haber, 2003, Pennartz et al., 2011). Specifically, the NAc, which is typically associated with limbic areas, regulates affective components of behavior, including motivational and emotional processes (Berke and Hyman, 2000, Meredith et al., 2008, Pennartz et al., 2011). Neurons in the NAc core and NAc shell subdivisions also differ functionally. The NAc core is involved in the processing of conditioned stimuli whereas the NAc shell is more important in the processing of unconditioned stimuli; these differences are thought to be due to variations in the morphology (shell neurons are smaller and significantly less spiny) and projection patterns of these subregions (Heimer et al., 1997, Groenewegen et al., 1999, Meredith et al., 2008). In contrast, the dorsal striatum, which contains both dorsomedial and dorsolateral aspects, receives dense innervation from neocortical areas, including motor areas (Berke and Hyman, 2000). The dorsomedial striatum is important in the performance of goal-directed behaviors whereas the dorsolateral striatum regulates habitual behaviors (Everitt and Robbins, 2005, Pennartz et al., 2011). Nonetheless, the striatal sub-regions are not independent, as limbic and cortical information can be passed from the NAc shell, through the core, and to the dorsal striatum in an ascending spiral via midbrain dopamine neurons (Haber et al., 2000).

Historical perspectives on how striatal circuitry regulates addiction

Studies using classical methods (e.g., electrolytic and excitotoxic lesions, pharmacological agonists and antagonists, microdialysis) have implicated both glutamate and dopamine transmission within the striatum in the development and persistence of addiction. For example, microdialysis studies have shown increases in the concentration of these neurotransmitters within the striatum following both acute and chronic drug exposure as

well as during relapse of drug-seeking behavior (Di Chiara and Imperato, 1988, Pierce et al., 1996, for review see Torregrossa and Kalivas, 2008). In addition, correlative studies utilizing immediate early gene expression as a marker of neuronal activation indicate the involvement of the striatum, together with its source regions of glutamate (prefrontal cortex [PFC], thalamus, amygdala and hippocampus) and dopamine (VTA and SNr), in addiction-related behaviors, including relapse and psychomotor sensitization (Table 2, Neisewander et al., 2000, Ciccocioppo et al., 2001, Ostrander et al., 2003, Kelley et al., 2005, Kufahl et al., 2009). Furthermore, lesions and pharmacological manipulations (e.g., non-selective agonists and antagonists, temporary inactivation) have confirmed a causal role for all of these regions in psychomotor sensitization and drug-taking and -seeking behaviors (Roberts and Koob, 1982, Wolf et al., 1995, Li and Wolf, 1997, Weissenborn et al., 1998, Tzschentke and Schmidt, 2000, McFarland and Kalivas, 2001, Shalev et al., 2002, Capriles et al., 2003, McFarland et al., 2003, See et al., 2007). Importantly, glutamatergic and dopaminergic projections into the striatum also appear to be critical for reinstatement of drug-seeking (Table 2) as pharmacological blockade of glutamate and dopamine receptors in the striatum prevents relapse (Park et al., 2002, Anderson et al., 2003, Bachtell et al., 2005). However, some of these studies have produced conflicting results, which is likely due to the non-specific nature of these techniques. Furthermore, these classical methods have not allowed us to parse apart the role of specific striatal afferent and efferent projections in addiction-related behaviors. To further complicate understanding the role of striatal circuitry in addiction, the neuronal populations within the striatum are physically intertwined, making manipulations to the distinct cell types difficult with traditional approaches and consequently limiting our knowledge of the role that each of the striatal cell populations play in the processes that govern addiction.

Thus, while lesions and pharmacological manipulations have given us insight into the broad nature of striatal circuitry regulation in addiction, these techniques lack both temporal and cellular specificity. Moreover, lesions and pharmacological manipulations cause widespread effects (e.g., effect fibers of passage), and these approaches cannot parse apart the function of specific afferent and efferent projections. Given the vast interconnectivity of this circuit, isolating the role of individual projections is critical for gaining a complete understanding of the neural mechanisms underlying addiction. Fortunately, the emergence of novel molecular and genetic technologies, such as DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) and optogenetics (Table 1), has provided new methods for exploring the relationship between neural activity and addiction-related behaviors and is giving us new insight into how specific cell types and projections within the cortico-basal ganglia-thalamic circuit regulate addiction. In the following sections we will discuss recent studies that utilize these techniques to parse apart the role of striatal afferent and efferent projections in regulating addiction-like behaviors.

The role of striatal direct and indirect MSNs in addiction

As described above, the classic model of cortico-basal ganglia-thalamic circuit function proposes that the direct and indirect pathways act in an opposing, yet balanced, manner to guide a variety of behaviors, including motor- and action-planning, decision-making, and motivation. As these pathways serve to optimize behavior outcomes, it has been

hypothesized that an imbalance between signaling in dMSNs and iMSNs may contribute to neuropsychiatric diseases, such as addiction (Lobo and Nestler, 2011, Smith et al., 2013, Volkow et al., 2013). However, until recently, it has been difficult to systematically study the contributions of these two striatal pathways to both normal and pathological behaviors. The advancement of molecular and genetic tools, including cell-specific viral-mediated gene transfer, expression of targeted toxins, fluorescent reporter mice, transgenic mice, and the development of novel classes of receptors, channels and calcium indicators are providing us with a means for visualizing and transiently altering neuronal activity in a highly selective manner. Thus, advancements in technology are now allowing us to begin to untangle the role of these striatal output pathways in behavior. For example, selective activation of dorsal striatal dMSNs, via light activation of channelrhodopsin 2 (ChR2, Table 1), initiates movement and reduces freezing in an open field while selective activation of dorsal striatal iMSNs decreases movement and increases freezing behavior (Kravitz et al., 2010). These data suggest that these two pathways do indeed work in opposition to promote normal behavior, as has previously been hypothesized. Next we will discuss the role of dMSNs and iMSNs in regulating addiction-related behaviors.

Effects of cocaine on neuronal signaling in direct and indirect striatal neurons

There is abundant evidence that psychostimulants such as cocaine induce different cellular and molecular adaptations in dMSNs and iMSNs (for review see Lobo and Nestler, 2011). It has remained unclear, however, what effect these drugs have on the temporal dynamics of neuronal signaling *in vivo* in these different neuronal populations. This issue was recently addressed with *in vivo* optical imaging studies (Table 1) using a fluorescent calcium indicator in reporter mice that expressed green fluorescent protein (GFP) in either dMSNs or iMSNs to measure cocaine-induced changes in intracellular calcium responses (a measure of neuronal activation) of dorsal striatal MSNs in naïve and chronically cocaine-treated mice (Luo et al., 2011, Park et al., 2013). An injection of cocaine in naïve mice increased the concentration of calcium in dMSNs while simultaneously decreasing the concentration of calcium in iMSNs; thus, shifting the balance of signaling to dMSNs (Luo et al., 2011). Although an injection of cocaine in mice chronically treated with cocaine resulted in blunted calcium responses in both dMSNs and iMSNs, this blunted effect was longer lasting in iMSNs, resulting in a net shift in the predominance of signaling to dMSNs (Park et al., 2013). Interestingly, chronically treated mice also displayed a decrease in baseline calcium events in iMSN (but not dMSNs), suggesting repeated cocaine exposure produces a generalized chronic shift in signaling to dMSNs. Together these data indicate that both acute and repeated cocaine exposure shifts the predominance of neuronal signaling to the direct pathway, and this altered balance in striatal pathway activity may facilitate continued drug use in addicts.

Role of direct pathway MSNs in addiction-related behaviors

There is considerable evidence implicating a role for dMSNs in drug reward. For example, antagonism of dopamine D1 receptors, which are predominately expressed in dMSNs, blocks expression of a cocaine conditioned place preference (CPP, Table 2) (Hiroi and White, 1991, Baker et al., 1998). However, it was not until recently that cell-specific

technologies have allowed us to expand upon these findings to understand the functional role of dMSNs in reward and motivation.

In particular, it was found that pairing optogenetic activation (via ChR2) of NAc core and shell dMSNs with a subthreshold dose of cocaine during conditioning produced a place preference for the cocaine-paired compartment (Lobo et al., 2010). Importantly, stimulating NAc core and shell dMSNs in the absence of cocaine did not result in a preference for the laser-paired chamber suggesting that the preference for the cocaine-paired chamber was not simply driven by a preference for laser stimulation. Nonetheless, it has been shown that optogenetic activation of *dorsal striatum* dMSNs is inherently reinforcing, because mice will work to receive stimulation of dMSNs in this area and laser stimulation of these neurons in a CPP paradigm is sufficient to induce a preference for the laser-paired chamber (Kravitz et al., 2012). Although these differences in behavior could be due to variation in stimulation parameters, they may also reflect a differential role in reward processing played by each striatal subregion. Consistent with the Lobo et al. (2010) findings, transient inhibition of synaptic transmission in NAc core and shell dMSNs during cocaine conditioning, via doxycycline-dependent expression of tetanus toxin, attenuated the development of a cocaine-induced place preference (Hikida et al., 2010). Together these data suggest that dMSN activity regulates the rewarding effects of cocaine.

In order to assess the role of dMSNs in drug-induced psychomotor sensitization, another paradigm commonly used to study the mechanisms underlying addiction, we used a cell-type specific chemogenetic DREADD receptor approach to ask whether decreasing neuronal excitability of dorsal striatal dMSNs would inhibit this behavior. We found that decreasing activity of dMSNs by activation of $G_{i/o}$ -coupled DREADDs during repeated amphetamine treatment blocked the persistence of locomotor sensitization (Ferguson et al., 2011). In line with these results, both optogenetic inhibition of NAc core and shell dMSNs and reversible blockade of neurotransmission in NAc core and shell dMSNs attenuated the development of cocaine-induced locomotor sensitization (Hikida et al., 2010, Chandra et al., 2013). Interestingly, although optogenetic stimulation of NAc core and shell dMSNs had no effect on baseline locomotor activity in drug-naïve mice, optogenetic stimulation was sufficient to produce a locomotor response in mice that had received repeated cocaine treatment, suggesting an increase in the reactivity of dMSNs to stimulation following cocaine exposure (Lobo et al., 2010).

While these studies have led to a better understanding of the role of dMSNs in the rewarding and psychomotor sensitizing effects of drugs, there has only been one study to date that directly assessed the role of dMSNs in an animal model of relapse. It was found that optical inhibition of NAc core projections to the SNr (i.e., those from dMSNs) failed to alter cocaine-plus-cue-induced reinstatement behavior (Stefanik et al., 2013). Nonetheless, it is possible that dMSNs may play an important role in different triggers of relapse, such as stress- or context-induced reinstatement, as these different types of relapse are thought to rely on dissociable, though overlapping, neural circuitry (Cardinal et al., 2002, Bossert et al., 2013). It will be important in future studies to parse out the role of dMSNs in other instigators of drug relapse (Table 2).

Role of indirect pathway MSNs in addiction-related behaviors

In opposition to the direct pathway, which acts as a ‘go’ signal to promote behavior, it is thought that the indirect pathway acts as a ‘brake’ to stop or inhibit behavior (Albin et al., 1989, Gerfen and Surmeier, 2011). While the focus of much work has been on the role of dMSNs in modulating addictive behavior, there is also mounting evidence that iMSNs play a role in motivation and addiction (Lobo and Nestler, 2011, Grueter et al., 2013). For example, optogenetic activation of NAc core and shell iMSNs suppressed the development of a cocaine CPP whereas selective ablation of NAc core and shell iMSNs via Cre recombinase-mediated expression of diphtheria toxin (Table 1) enhanced the development and the persistence of an amphetamine CPP (Durieux et al., 2009, Lobo et al., 2010). These findings suggest that iMSNs can bidirectionally modulate drug reward.

To assess the role of iMSNs in amphetamine-induced psychomotor sensitization, we used activation of $G_{i/o}$ -coupled DREADDs to transiently reduce activity of dorsal striatum iMSNs during an amphetamine sensitization protocol that normally produces threshold levels of sensitization (Ferguson et al., 2011). We found that decreasing activity of iMSNs during repeated amphetamine exposure enhanced the development and persistence of sensitization. Consistent with these results, both optogenetic and chemogenetic activation of NAc core and shell iMSNs, by Chr2 and G_s -coupled DREADDs respectively, during amphetamine treatment prevented the development and persistence of locomotor sensitization (Chandra et al., 2013, Farrell et al., 2013). In addition, optogenetic activation of NAc core and shell iMSNs during drug withdrawal subsequently attenuated the expression of sensitization to cocaine, suggesting that neuroplastic changes, such as changes in gene expression and synaptic remodeling, in iMSNs during drug withdrawal are critical for the persistence of this addiction-related behavior (Song et al., 2014).

Recently, the role of iMSNs in the motivation to self-administer cocaine (Table 2) has been explored, and it was found that optogenetic activation of iMSNs in the NAc core suppressed cocaine self-administration while inhibition of NAc core (but not dorsal striatum) iMSNs via activation of $G_{i/o}$ -coupled DREADDs enhanced the motivation to take cocaine, as measured by a progressive ratio test (Table 2, Bock et al., 2013). Importantly, these results were not driven by a general increase in motivation because inhibition of iMSNs had no effect on responding for a food reward. Interestingly, these researchers also examined changes in synaptic plasticity in MSNs following cocaine self-administration and found that all mice exhibited synaptic potentiation of glutamatergic inputs onto dMSNs, but this potentiation was only seen in iMSNs in mice that did not show compulsive behaviors (defined in Table 2) following drug use (Bock et al., 2013). Together these data suggest that iMSNs normally act to restrain drug-taking behavior and recruitment of these neurons may in fact be protective against the development of compulsive drug use.

The role of iMSNs has also been examined in relapse of drug-seeking behavior and it was found that optical inhibition of NAc core projections to VP (i.e., those from iMSNs) attenuated cocaine-plus-cue-induced reinstatement (Stefanik et al., 2013). Although this finding is in contrast to the series of studies discussed above showing that iMSNs normally act to inhibit cocaine reward and behavioral sensitization, it suggests that the indirect pathway regulates addiction-related behaviors in a more complex manner than the traditional

“go-brake” model would predict. Nonetheless, as described earlier, there is considerable evidence that projections through the NAc core indirect striatal pathway arise from both dopamine D1- and D2-expressing neurons (for review see Smith et al., 2013). It may be that D1- and D2-expressing NAc core MSNs that project to the VP differentially regulate reinstatement of drug-seeking, but additional studies would be needed to parse this out, as it cannot be determined from the optogenetic approach utilized by Stefanik et al. (2013).

The role of striatal dopamine inputs in addiction

Both the NAc and the dorsal striatum receive dense innervation from midbrain dopamine neurons, and these inputs have long been implicated in addictive behaviors (Swanson, 1982, Robinson and Berridge, 1993, Berke and Hyman, 2000, Everitt and Robbins, 2005, Gerfen and Surmeier, 2011). In particular, the primary pharmacological effects of psychostimulants are on dopamine release and reuptake mechanisms and while not their primary site of action, all other classes of abused drugs also increase striatal dopamine levels (Di Chiara and Imperato, 1988, White and Kalivas, 1998, Willuhn et al., 2010, Vander Weele et al., 2014). Since dMSNs express excitatory, G_s/oI_f -coupled dopamine D1 receptors and iMSNs express higher affinity, inhibitory $G_{i/o}$ -coupled dopamine D2 receptors, drug-induced dopamine release has opposite effects on these two classes of MSNs. In addition, dopamine can have profoundly different effects on the plasticity of cortical inputs to these two striatal cell populations (Gerfen and Surmeier, 2011, Baik, 2013). For example, rewarding events (e.g. drug-taking) lead to dopamine release in the striatum, which promotes long-term potentiation (LTP) in cortical synapses onto dMSNs while simultaneously producing long-term depression (LTD) in iMSNs. Conversely, during non-rewarding events, dopamine neurons pause, resulting in decreased dopamine release in the striatum, which increases the strength of cortical synapses onto iMSNs and reduces the strength of cortical synapses onto dMSNs (Reynolds et al., 2001, Tang et al., 2001, Calabresi et al., 2007, Kreitzer and Malenka, 2007, Cohen and Frank, 2009, Gerfen and Surmeier, 2011, Hong and Hikosaka, 2011).

Recent advances in neurotransmitter detection, such as fast scan cyclic voltammetry (FSCV, Table 1), are now allowing us to detect *in vivo* dopamine release in the striatum on a sub-second scale time resolution thereby providing a means for studying the temporal dynamics of phasic dopamine signaling. This method has highlighted that contingent versus non-contingent drug administration results in different patterns of dopamine signaling in the NAc core (Stuber et al., 2005). In addition, it has been found that phasic signaling events occur to both cues and drugs during drug-seeking and drug-taking behaviors, and surprisingly these events are actually larger for the drug-associated cues (Phillips et al., 2003, Stuber et al., 2005). More recently, FSCV has been used to track phasic dopamine signals to drug-associated cues over time, and it was shown that phasic dopamine signaling patterns in the striatum vary across subregion (i.e., ventromedial and dorsolateral striatum) and by stage of drug-taking (i.e., early vs. late), but decline in response to escalating cocaine administration (Willuhn et al., 2012, Willuhn et al., 2014). FSCV, therefore, has proven important for disentangling the role of phasic dopamine signaling in the striatum in motivated behaviors and learned associations during addiction-related behaviors.

Although novel technologies are now allowing us to demonstrate the importance of midbrain dopamine in reward behaviors (see Lenz and Lobo, 2013 for review), surprising little has been done to investigate the role of dopaminergic projections to the striatum in addictive behaviors. In one study, combining optogenetic stimulation of VTA terminals in the NAc with a subthreshold dose of morphine during conditioning produced a CPP for the morphine-paired compartment (Koo et al., 2012). In addition, optical inhibition of VTA projections to the NAc core significantly reduced cocaine-plus-cue induced reinstatement (Table 2, Stefanik et al., 2013). These findings fit with dopamine's purported role in motivation and reward and emphasize the necessity for future investigations into the role of specific dopaminergic projections in reward and addiction.

Role of striatal glutamatergic afferents in addiction

The striatum not only receives dense dopamine projections from the VTA and SNr, but it also receives innervation from glutamatergic projection neurons originating in multiple brain regions. Each of these glutamatergic inputs is thought to regulate distinct aspects of the behaviors associated with addiction (Sesack and Grace, 2010). The cortex is the predominant source of striatal glutamate and corticostriatal projections display topographic specificity, such that more dorsolateral regions of the striatum receive projections from sensorimotor cortex and more ventromedial portions of the striatum receive projections from associative cortex, including PFC (McGeorge and Faull, 1989, Groenewegen et al., 1990, Koob and Volkow, 2010, Sesack and Grace, 2010, Wall et al., 2013). Within the NAc, the PFC projections can be further subdivided with the infralimbic region projecting primarily to the NAc shell and the prelimbic region projecting primarily to the NAc core (Sesack et al., 1989, Brog et al., 1993). In addition, cortical neurons can be split into two subtypes based on their projection targets. Intratelencephalic (IT-type) neurons project both ipsilaterally and bilaterally within the telencephalon whereas pyramidal tract (PT-type) neurons project to the brainstem and send collaterals throughout the brain, including to the striatum. IT-type neurons are thought to synapse primarily on dMSNs whereas PT-type neurons are thought to project primarily to iMSNs (Reiner et al., 2010, Shepherd, 2013, but see Kress et al., 2013).

The second largest source of striatal glutamate originates in the thalamus (Lei et al., 2013, Wall et al., 2013). Midline and intralaminar thalamic structures, including the paraventricular nucleus, mediodorsal, central median, and parafascicular nuclei, send dense glutamatergic projections to the striatum and synapse directly onto both dMSNs and iMSNs (Berendse and Groenewegen, 1990, Li and Kirouac, 2008, Haber and Calzavara, 2009, Lei et al., 2013, Wall et al., 2013). Finally, the amygdala and hippocampus provide glutamatergic inputs mostly to ventral striatum and both of these projections appear to synapse primarily on dMSNs (Groenewegen and Trimble, 2007, Britt et al., 2012, MacAskill et al., 2012, Pascoli et al., 2012, Wall et al., 2013, MacAskill et al., 2014). Although new technologies are being used to refine the role of each of these sources of striatal glutamate in addiction-related behaviors, in this section we will focus on the studies that specifically probed the role of the glutamatergic afferents into the striatum.

Prefrontal Cortex

Dysregulation of the PFC following drug use is widely believed to underlie the loss of inhibitory control seen in drug addicts and is a primary contributing factor in relapse (Kalivas, 2009, Goldstein and Volkow, 2011). Work in rodent models has found that the prelimbic and infralimbic areas of the PFC are particularly important for regulating drug-seeking and the expression of addiction-related behaviors such as psychomotor sensitization and discrimination between levers during self-administration paradigms (Seamans et al., 2008, Francis et al., 2014, Moorman et al., 2014, Pascoli et al., 2014).

Although the PFC has widespread and reciprocal projections within the cortico-basal ganglia-thalamic circuit, recent studies support the idea that both drug-induced neuroplasticity in MSNs and drug-induced behaviors are modulated specifically by PFC afferents to the NAc shell. For example, infralimbic inputs to the NAc shell were found to undergo silent synapse based remodeling following withdrawal from cocaine self-administration that was dependent on the insertion of calcium-permeable AMPA receptors, and reversal of this silent-synapse based remodeling via optical stimulation enhanced cue-induced cocaine seeking (i.e., incubation of craving, Table 2) (Ma et al., 2014). Similarly, using optical stimulation of infralimbic terminals within the NAc shell of fluorescently-labeled dopamine D1 or dopamine D2 BAC transgenic mice, it was found that withdrawal from cocaine self-administration resulted in enhanced glutamatergic signaling in D2 MSNs (dMSNs) but not D1 MSNs (iMSNs) that was also due to insertion of calcium-permeable AMPA receptors (Pascoli et al., 2014). Although using an optical stimulation LTD protocol to restore normal transmission selectively in these inputs prior to cue-induced reinstatement also increased lever responding, it did so non-discriminatively (Pascoli et al., 2014). Nonetheless, using this method to normalize transmission prior to a cocaine challenge was sufficient to block the expression and persistence of cocaine-induced locomotor sensitization (Pascoli et al., 2012).

Studies have also begun to explore the role of PFC inputs into the NAc core in addiction-related plasticity and behavior. Similar to the NAc shell, withdrawal from cocaine self-administration also produced silent synapse remodeling in prelimbic inputs to NAc core MSNs, but this occurred via a mechanism that was dependent on non-calcium permeable AMPA receptor insertion (Ma et al., 2014). Furthermore, reversal of this silent-synapse based remodeling via optical stimulation inhibited cue-induced cocaine seeking (Ma et al., 2014). Likewise, optical inhibition of prelimbic afferents to the NAc core during reinstatement reduced cocaine seeking during both cocaine-primed reinstatement and cocaine-plus-cue-induced reinstatement (Stefanik et al., 2013, Stefanik et al., 2015).

It is likely that these post-synaptic neuroadaptations at corticostriatal synapses are at least partly due to drug-induced presynaptic alterations in neurotransmitter release. In support of this, optogenetic stimulation of PFC inputs to the NAc shell following either contingent or non-contingent cocaine administration revealed an increase in release probability at both short and long withdrawal periods, although the probability of neurotransmitter release was higher in mice that had self-administered cocaine compared to those that had received experimenter-administered drug (Suska et al., 2013).

Together, these studies support the idea of dissociable roles of PFC projections to the NAc core and shell in regulating addiction behavior and associated plasticity, although it is clear that the manner in which they do so is complex. In addition, it should be noted that changes in plasticity at corticostriatal synapses within the NAc are not always observed following repeated drug treatment (Britt et al., 2012). Multiple factors, including amount of drug intake, contingency of drug administration and withdrawal time influence the neurobiological changes that occur following drug use. Likewise, experimental variables such as optical stimulation parameters and the subset of cells that are targeted within a striatal or cortical region can also have a big impact on experimental outcomes. Thus, additional work to normalize such variables will be required to gain a full understanding of the role cortical inputs into striatum play in addiction processes.

Amygdala

The amygdala is thought to regulate conditioned responses to cues associated with drug-taking (Goldstein and Volkow, 2002, Kalivas and Volkow, 2005, Bossert et al., 2013). However, relatively few studies have directly assessed neurobiological changes in amygdala projections to striatum and their contribution to addiction-related behavior. Following a cocaine sensitization protocol, it was found that optogenetic stimulation of basolateral amygdala (BLA) inputs to the NAc shell selectively enhanced excitatory post-synaptic currents and increased spine density in dMSNs, suggesting that cocaine-induced alterations in dMSN function and structure are due to an increase in the strength of BLA inputs to these neurons (MacAskill et al., 2014). However, other studies using optical stimulation of BLA inputs to the NAc shell following either cocaine self-administration or behavioral sensitization did not observe alterations in plasticity of striatal neurons (Suska et al., 2013, Pascoli et al., 2014). Nonetheless, these striatal glutamatergic afferents from the BLA appear to regulate incubation of craving and drug-seeking. For example, following cocaine self-administration and extinction, optical inhibition of BLA inputs to the NAc core during cue-induced reinstatement decreased cocaine-seeking (Stefanik and Kalivas, 2013). In addition, it was found that the incubation of cue-induced cocaine seeking normally seen following prolonged withdrawal could be blocked by an optical stimulation LTD protocol that reversed the maturation of silent synapses in BLA inputs to the NAc shell (Lee et al., 2013). Thus, while the extent to which BLA projections to the striatum contribute to changes in MSN plasticity is unclear, there is ample evidence to support the role of these projections in regulation of the development of conditioned responses to cues associated with drug-taking as well as drug-craving. Therefore, these projections are a strong candidate for therapeutic interventions that could mitigate relapse.

Hippocampus

The hippocampus is thought to be involved in the formation of associations related to the context associated with drug-taking and may regulate the strength of responding during reinstatement (Koob and Volkow, 2010, Francis et al., 2014, Pascoli et al., 2014). Optical stimulation of ventral hippocampus afferents to the NAc shell paired with electrophysiology recordings from fluorescently-labeled dopamine D1 receptor or dopamine D2 receptor BAC transgenic mice demonstrated that cocaine self-administration increased synaptic plasticity of these inputs onto dMSNs but not iMSNs (Pascoli et al., 2014). Alterations in synaptic

plasticity within the NAc shell MSNs at ventral hippocampus synapses have also been observed following behavioral sensitization to cocaine (Britt et al., 2012). In addition, optical inhibition of ventral hippocampus terminals in the NAc shell blocked cocaine sensitization whereas optical stimulation enhanced this behavior (Britt et al., 2012). Furthermore, optical stimulation of these projections is rewarding in and of itself, as evidenced by the development of a CPP for a chamber paired with light stimulation (Britt et al., 2012). Finally, using an optical stimulation LTD protocol to restore normal transmission selectively in hippocampal inputs to the NAc shell prior to cue-induced reinstatement resulted in decreased cocaine-seeking (Pascoli et al., 2014). Additionally, cocaine-seeking was completely abolished when normal transmission was restored to both PFC and hippocampal inputs (Pascoli et al., 2014). Together, these studies provided evidence that drug exposure increases synaptic plasticity in ventral hippocampus projections to dMSNs, which leads to an enhancement in contextual-mediated associations within the drug-taking environment. However, in contrast to these findings, ventral hippocampal inputs to the NAc shell were actually dampened in dMSNs three days after a sensitizing regimen of cocaine (MacAskill et al., 2014). These discrepant findings may reflect a differential involvement of ventral hippocampus in early versus late withdrawal, as well as differences in experimental parameters.

Thalamus

Although the thalamus densely innervates the striatum, it has largely been overlooked when studying the circuitry underlying addiction. Nonetheless, mounting evidence suggests that thalamic impairments contribute to the sensory processing and attentional deficits seen in addicts, and may also modulate drug-craving and other addiction-related behaviors (Koob and Volkow, 2010, Martin-Fardon and Boutrel, 2012, James and Dayas, 2013). For example, cFos is upregulated in the paraventricular nucleus of the thalamus (PVT) following an acute injection of either cocaine or amphetamine as well as after exposure to drug-associated cues or contexts (Deutch et al., 1998, Hamlin et al., 2009, Rotllant et al., 2010, James et al., 2011). Furthermore, lesions of the PVT enhance the acute locomotor response to an injection of cocaine, but block psychomotor sensitization and prevent context-induced reinstatement (Young and Deutch, 1998, Hamlin et al., 2009). The mediodorsal nucleus of the thalamus (MD) has also been implicated in regulating responses to psychostimulants, as lesions of the MD attenuate cocaine intake during self-administration (Weissenborn et al., 1998). However, despite evidence indicating that mediodorsal thalamus (MD) neurons are active during cue-induced reinstatement, inactivation of MD did not alter cocaine-primed or stress-induced reinstatement (McFarland and Kalivas, 2001, McFarland et al., 2004, James et al., 2011). These data suggest that the various midline thalamic nuclei may differentially regulate aspects of addiction-related behavior. However, even though the thalamus sends a strong glutamatergic projection to the striatum, there have been no studies to date utilizing more recent technology that allow for precise temporal and spatial control to define the specific role of these thalamic projections in addiction.

Concluding Remarks

This review has focused on how the emergence of new technologies is refining our understanding of the ways in which striatal cell populations are engaged by drugs and associated stimuli, and how striatal afferents and efferents regulate the development of behaviors related to addiction. In particular, we have explored how targeted approaches are now allowing us to visualize (e.g., FCSV, calcium imaging) and manipulate with high spatial and temporal resolution (e.g., DREADDs, optogenetics) processes that are occurring at the cell-specific and/or synapse-specific level in order to map the connections that govern addiction. Although this work is just beginning, it is evident that the circuit is more complex and dynamic than has been revealed previously. In addition, it is now clear that the pattern and source of dopamine and glutamate neurotransmission is as critical, if not more so, than the absolute level for shaping drug-induced neuroplastic events and related behaviors. Nonetheless, we know that variations in behavioral paradigms and technique parameters can have a huge impact on experimental outcomes, therefore, systematic studies that carefully control for these variables must be conducted before definitive conclusions can be drawn.

An imbalance between direct and indirect striatal pathway activity has been hypothesized to mediate a transition to addiction, and current work utilizing cell-specific approaches supports this idea. However, given that dMSNs send axon collaterals to outputs of the indirect pathway and many of the studies described in this review utilized techniques that manipulated dMSNs at the level of the striatum, it will be necessary to perform experiments in the target regions of dMSNs and iMSNs to fully resolve the contributions of these two pathways in addiction behaviors. Recent anatomical studies have revealed that glutamatergic projections, both within and across structures, display differential selectivity for dMSNs and iMSNs and raise the intriguing possibility that the direct and indirect pathways should be extended to include these afferent inputs. Future studies will be necessary to determine whether other striatal afferents share this preferential innervation of a particular striatal cell type, as well as what the functional implications of extending these pathways are to addiction.

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Highlights

- Circuit regulation of addiction is complex and dynamic.
- The pattern and source of dopamine and glutamate neurotransmission in striatum is critical for shaping addictive processes.
- Novel techniques are providing new insights into the neural circuits that regulate addiction.

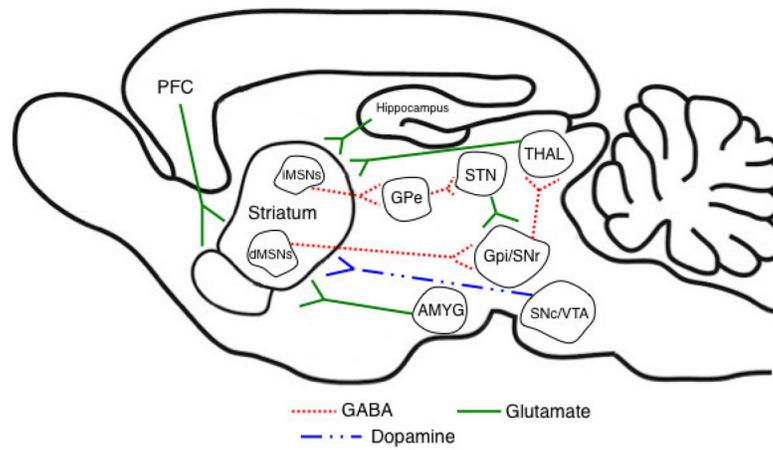


Fig. 1. Simplified schematic view of striatal inputs and outputs. The striatum receives glutamatergic inputs (denoted in green) from the cortex, amygdala, hippocampus and thalamus and dopaminergic inputs (denoted in blue) from the VTA and SNc. Direct pathway striatal neurons (dMSNs) project monosynaptically to the GPi/SNr whereas indirect pathway striatal neurons (iMSNs) project to the GPi/SNr via the GPe/VP and STN. Red dashed lines denote GABAergic inhibitory projections.

Table 1

Glossary Term	Description	Citation
Conditioned Place Preference (CPP)	Pavlovian conditioning used to measure the rewarding (or aversive) properties of drugs. During conditioning, rodents receive non-contingent injections of drug and saline in two distinct chambers. Testing consists of free access to both the saline-paired and drug-paired chamber, and often a third, unpaired (neutral) area. A drug is considered to be rewarding if the most time is spent in the drug- paired chamber, and aversive if the least amount of time is spent in the drug-paired chamber.	Huston (2013) Tzschentke (1998) Bardo (2000)
Psychomotor sensitization	An increase in the behavioral effects (i.e., locomotor activity or stereotypies) of a drug that occurs with repeated exposure. Rodents receive repeated injections of drug non-contingently, and responses to the same dose of the drug increase over sessions. Following a period of withdrawal, animals receive a drug injection, and behavioral responses are greater in rodents that have received prior drug treatment compared to animals that are receiving the drug for the first time. Psychomotor sensitization can be used as a behavioral read-out of an underlying neural sensitization in addiction circuits.	Steketee (2011) Robinson (2008) Robinson (2000)
Drug self- administration	Response-dependent administration of drug. Rodents learn that performing an operant response (e.g., lever press or nosepoke) on the active lever/port results in drug infusion whereas responses on the inactive lever/port does not. Responses on active lever/port are higher than on inactive lever/port in animals that learn to self-administer drug.	Belin-Rauscent (2015) Panlito (2007) Everitt (2005)
Progressive Ratio	A schedule of reinforcement used to assess the motivation to take drugs during drug self- administration. Progressive ratio testing consists of increasing the response requirement for each subsequent drug infusion. The point at which an animal ceases to respond is termed the breakpoint. Higher breakpoints indicate higher levels of motivation to obtain drug.	Stafford (1998)
Compulsive behavior	Repetitive behaviors that develop over time. In the context of drug self-administration, compulsive drug-seeking can be defined by two different behaviors: 1) perseverance of drug-seeking when drug is not available, assessed by measuring responding during signaled drug-unavailable periods and 2) motivation to obtain drug, evaluated using a progressive ratio schedule of reinforcement. Compulsive animals show perseverance of cocaine seeking and higher breakpoints compared to non-compulsive mice.	Bock (2013)
Drug Craving	An affective state that can be produced following exposure to a drug, drug-associated cues or stress. In self-administration models, craving is inferred by a behavioral response (e.g. lever pressing or nose pokes). Higher behavioral responses suggest higher levels of craving.	Pickens (2011) Marchant (2013) Li (2015)
Incubation of drug craving	A hypothetical motivational construct based on findings that cue-induced operant responding increases in proportion to the length of withdrawal that followed drug self-administration. More drug seeking is observed with longer periods of abstinence.	Pickens (2011) Marchant (2013) Li (2015)
Reinstatement of drug-seeking	Model of relapse. Rodents learn to self-administer a drug, which is followed by extinction of responding. Subsequent presentation of drug-paired stimuli (e.g., cue, drug, or context) or a stressor restores operant responding.	Marchant (2013) Bossert (2013) Epstein (2006)

Table 2

Technique	Action	Timecourse	Specific approach	Effect on neuron	Citation
Diphtheria toxin	Activation of the diphtheria toxin receptor by diphtheria toxin induces cell death via inhibition of protein synthesis	Permanent	NA	Cell death	Buch (2005) Huang (2013)
DREADDs (Designer Receptors Exclusively Activated by Designer Drugs)	Mutated muscarinic receptors that are activated by the otherwise inert ligand clozapine-N-oxide (CNO) to increase G-protein coupled receptor signaling cascades and alter neuronal function	Minutes to hours	hM ₄ D(G _i) rM ₃ D(G _s) hM ₃ D(G _q)	Activation of G _{1/0} signaling cascades leads to a reduction in neuronal firing Activation of G _s or G _q signaling cascades leads to an increase in neuronal firing	Urban & Roth (2014) Ferguson & Neumaier (2015)
Fast-scan cyclic voltammetry (FSCV)	Electrochemical technique used to detect changes in the concentration of extracellular dopamine	Subsecond	NA	None	Willuhn (2010) Robinson (2003)
<i>In vivo</i> calcium imaging	Measures changes in the concentration of intracellular calcium via fluorescent microscopy	Millisecond	Rhod	Rhodamine-based indicator that increases fluorescence when bound to calcium	Grienberger & Konnerth (2012)
Optogenetics	Optical activation of light sensitive channels (opsins) triggers or inhibits action potentials	Millisecond	Channelrhodopsin (ChR2)	Optical stimulation of neuronal activity by increasing intracellular sodium	Tye & Deisseroth (2012) Zalocusky & Deisseroth (2013) Allen et al (2015)
			Archaeorhodopsin (Arch)	Optical inhibition of neuronal activity by pumping protons out of cell	
			Halorhodopsin (eNpHR)	Optical inhibition of neuronal activity by increasing intracellular chloride	
Tetanus Toxin	Prevents neurotransmitter release from neurons expressing toxin by cleavage of vesicle associated membrane protein2 (VAMP2), which disrupts synaptic vesicle docking	Days to weeks	NA	Eliminates neurotransmitter release	Fowler & Kenny (2011)