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REVIEW

Reward Circuitry in Addiction

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Abstract Understanding the brain circuitry that underlies reward is critical to improve treatment for many common health issues, including obesity, depression, and addiction. Here we focus on insights into the organization and function of reward circuitry and its synaptic and structural adaptations in response to cocaine exposure. While the importance of certain circuits, such as the mesocorticolimbic dopamine pathway, are well established in drug reward, recent studies using genetics-based tools have revealed functional changes throughout the reward circuitry that contribute to different facets of addiction, such as relapse and craving. The ability to observe and manipulate neuronal activity within specific cell types and circuits has led to new insight into not only the basic connections between brain regions, but also the molecular changes within these specific microcircuits, such as neurotrophic factor and GTPase signaling or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor function, that underlie synaptic and structural plasticity evoked by drugs of abuse. Excitingly, these insights from preclinical rodent work are now being translated into the clinic, where transcranial magnetic simulation and deep brain stimulation therapies are being piloted in human cocaine dependence. Thus, this review seeks to summarize current understanding of the major brain regions implicated in drug-related behaviors and the molecular mechanisms that contribute to altered connectivity between these regions, with the postulation that increased knowledge of the plasticity within the drug reward circuit will lead to new and improved treatments for addiction.

Key Words Cocaine · reward · dopamine · glutamate · ventral tegmental area · nucleus accumbens

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Introduction

Understanding of the brain circuitry that mediates feelings of reward or pleasure is of great interest, with myriad papers published in the last few years identifying regions and connections associated with a variety of natural rewards, including food, sex, and social interaction. Many of these studies have taken advantage of increasingly sophisticated genetics-based tools to observe and manipulate neuronal activity within specific cell types and circuits to ascertain their role in reward processes. However, much of what we know of the structure of the reward circuit, and the generation of pleasure, was originally identified in the context of drugs of abuse. Thus, our understanding of the circuitry underlying the rewarding aspects of drug use, and maladaptive reward underlying addiction, informs the greater understanding of general reward mechanisms. Moreover, while some specific nodes of the reward circuitry, such as dopamine (DA) outputs from the ventral tegmental area (VTA) to nucleus accumbens (NAc), and their importance to drug reward, are well established, our understanding of the complexity of the reward circuit underlying various aspects of addiction, such as relapse and craving, has increased through the use of "circuit-busting" opto- and chemogenetic approaches. Thus, the goal of this review is to summarize the current understanding of the major players (brain regions) in drug reward and the role of the connections

between these regions (circuitry) in aspects relevant to addiction and to connect greater understanding of these reward circuit dynamics to potential improvements in the treatment of drug addiction.

Wiring of the Reward Circuitry

VTA

The general understanding of the reward circuitry underlying addiction begins with the VTA, a heterogeneous brain region composed largely of DA (60–65%) and γ-amino butyric acid (GABA; ~30–35%) neurons, with a smaller proportion of glutamatergic neurons (2–3%) [1, 2]. Most studies have focused on the VTA DA neurons, as stimulation of these neurons and the release of DA in projection sites, most notably the NAc, is known to produce reward. Early work has shown that virtually all known drugs of abuse increase DA release in the NAc [3], and blocking the action of the DA (via receptor blockade) blocks many behavioral effects of drugs [4]. Furthermore, VTA DA activation is sufficient to support self-stimulation and both noncontingent and contingent reward behavior, as has been recently demonstrated through the use of optogenetics (detailed below; [5–7]).

However, through tracing and functional studies, it has become clear that VTA DA neurons are not as homogenous as previously thought, and can be subdivided by projection target. The 2 most extensively studied VTA DA neuron subtypes to date are those that project to the NAc (mesolimbic) and prefrontal cortex (PFC; mesocortical), though there are additional projection sites, including the amygdala and hippocampus (Fig. 1). Current evidence suggests that VTA DA neuron subtypes have distinct electrophysiological properties and functional outcomes [8, 9]. For example, a rewarding stimulus (cocaine) selectively modulates excitatory input to VTA DA neurons that project to NAc, in contrast to an aversive stimulus (hindpaw formalin injection) that selectively modulates synaptic input onto VTA DA neurons that project to medial PFC (mPFC) [10]. Further, these differences are behaviorally relevant and constitute distinct microcircuits: activation of glutamatergic neurons in laterodorsal tegmentum synapsing onto VTA DA neurons projecting to NAc increases reward behavior, while activation of glutamatergic lateral habenula neurons that innervate VTA DA neurons that project to the mPFC induces aversive behavior [11]. The lateral habenula neurons also innervate GABA neurons in the rostromedial tegmentum nucleus, or "tail" of the VTA, which exert inhibitory tone specifically on VTA DA neurons projecting to NAc (Fig. 1) [11]. Critically, while it is increasingly clear that VTA DA neurons should be classified based on their connectivity, little is known about molecular differences between these subtypes of neurons. Future studies are likely to address this key issue, as molecular profiling techniques such as translating ribosome affinity purification, and more recently retro-translating ribosome affinity purification [12], have been pioneered and used to specifically isolate mRNA from VTA DA neurons that project to NAc [13], for example.

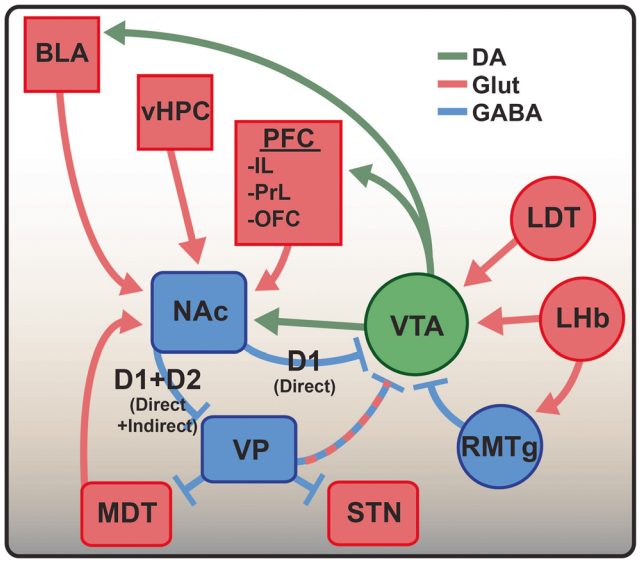

Fig. 1 Schematic of brain reward circuitry implicated in addiction. Dopaminergic (DA; green) and glutamatergic (Glut; red) inputs converge on γ-aminobutyric acid (GABA)ergic (blue) neurons in the nucleus accumbens (NAc) to coordinate and regulate drug-related behaviors. BLA = basolateral amygdala; D1 = dopamine type 1 receptor; D2 = dopamine type 2 receptor; LDT = laterodorsal tegmentum; LHb = lateral habenula; MDT = mediodorsal thalamus; PFC = prefrontal cortex; RMTg = rostromedial tegmentum; STN = subthalamic nucleus; Thal = thalamus; vHPC = ventral hippocampus; VP = ventral pallidum; IL = infralimbic; PrL = prelimbic; OFC = orbitofrontal cortex; VTA = ventral tegmental area;

While the focus of this review is on reward, and thus many of the studies discussed here focus on these VTA DA projection neurons, it is also clear that VTA GABA neurons are critical for reward processing. The role of these GABA neurons in reward and aversion has been elegantly demonstrated via optogenetics, where activation of VTA GABA neurons produces real-time aversion, and inhibition of these neurons produces preference. These effects are thought to depend largely on the activity of VTA GABA interneurons, as VTA GABA activation inhibited VTA DA neuronal activity and produced a concomitant decrease in DA release in NAc, while terminal activation of VTA GABA neurons in NAc was sufficient to increase GABA concentration but not to alter reward behavior [14, 15].

NAc

As described above, a major reward-related output of VTA DA activity is NAc, or ventral striatum. Here, DA can exert its effects via activation of DA receptors located on medium spiny

neurons (MSNs), the predominant cell type in NAc. MSNs are GABAergic projection neurons and consist of 2 (largely) separate classes defined by their expression of either D1- or D2-like DA receptors [16, 17]. D1 and D2 MSNs in the dorsal striatum are thought to have generally separate projections, with D1 MSNs constituting the "direct" pathway (ultimately increasing thalamocortical drive) and D2 MSNs forming the "indirect" pathway (ultimately decreasing thalamocortical drive). However, evidence suggests that this direct *versus* indirect pathway distinction is not as clear in NAc as it is in dorsal striatum, given that only NAc D1 MSNs project to the VTA, while both D1 MSNs and D2 MSNs project to the ventral pallidum (VP) (Fig. 1) [18, 19]. Investigation of the role of D1 *versus* D2 DA signaling in NAc and its role in addictive behavior has been of long standing interest in the field, initially through the use of agonists and antagonists [4], and more recently using optogenetic approaches [20]. In addition to the cellular heterogeneity (D1 *vs* D2 cells), there is also regional heterogeneity, with distinct drug-associated behaviors and plasticity differences noted between the NAc core and shell subregions [21]. MSNs in NAc core appear to be critical for assigning motivational value to discrete stimuli associated with reward or aversion, and particularly updating these values as circumstances change, while those in the NAc shell drive behavioral responses to repeated exposure to rewarding experiences, such as chronic drug administration [22]. While VTA DA neurons provide a strong modulatory input onto NAc MSNs, they also receive a large amount of glutamatergic input from a variety of limbic and cortical regions, some of the most notable being PFC, ventral hippocampus (vHIPP), and basolateral amygdala (BLA) (Fig. 1) [23, 24].

PFC

PFC input to NAc is largely associated with executive control and thought to mediate goal-directed behaviors such as the seeking and planning of action to obtain reward-related substances (like drugs of abuse) [25]. PFC subregions differ in their projections to NAc, with infralimbic (IL) mPFC preferentially projecting to NAc shell and prelimbic mPFC (PrL) to NAc core [23]. However, pharmacological and optogenetic manipulation of specific PFC inputs to NAc has shown that the cocaine-related synaptic plasticity and behavior differs between PFC subregions [26, 27]. This fascinating complexity is at the forefront of addiction research, and examples of these sometimes competing or complementary adaptations are described below (in "PFC–NAc Stimulation" subsection).

vHIPP

vHIPP also sends glutamatergic projections to NAc and is thought to act as a site of integration between spatial/contextual information from dorsal HIPP and emotional information from BLA and locus coeruleus [28–30]. Thus, the vHIPP–NAc connection acts to provide contextually relevant emotional information to influence goal-directed behavior. This circuit has been implicated in both reward and aversive behaviors, and its modulation has been shown to impact locomotor responses to drugs of abuse and cue-induced drug-seeking behavior [31, 32].

Amygdala

The amygdala also sends glutamatergic input to NAc, and its effects are thought to be mediated by D1 DA receptor activation [33, 34]. In particular, activation of BLA–NAc projections facilitates reward seeking and supports positive reinforcement [34, 35]. While there is a well-established role of amygdala activation in emotional learning, and for projections from the BLA in particular to mediate fear- and anxiety-behaviors, these effects appear to be mediated distinctly from those of BLA projections to NAc, as the BLA–NAc microcircuit drives reward and reinforcement [36].

Thalamus

More recently, glutamatergic inputs into NAc from subregions of the thalamus, and especially midline thalamic nuclei like the paraventricular nucleus (PVT), have been characterized. In contrast to glutamatergic inputs from the regions described above (vHIPP, PFC, amygdala) where stimulation is rewarding, direct activation of the PVT–NAc pathway is aversive, driving behavioral aversion in a real-time place preference assay [37]. Additionally, alteration of PVT activity has been shown to alter drug-related behaviors like cocaine reward and seeking [38–40]. These behavioral changes are likely driven by changes in drug-induced plasticity within the medial thalamus–NAc circuit, as cocaine experience has been shown to alter *N*-methyl-D-aspartate (NMDA) function and plasticity and increase silent synapses within this circuit, with plasticity changes dependent on both MSN cell type (D1 *vs* non-D1) and subregion (shell *vs* core) [41, 42].

Together, the regions described above form a highly integrated circuit, the cortico-basal ganglia reward network [23], with drug-induced changes in plasticity within the circuit contributing to various facets of addiction [43]. The function of this circuitry is made all the more complex by the fact that these many regions, and the specific projection neurons connecting them, experience a wide range of molecular and functional changes in response to drug exposure, often with opposing or seemingly contradictory effects on behavior.

Molecular Mechanisms of Drug-Evoked Synaptic and Structural Plasticity

It is well established that drug dependence and addiction involve changes in both synaptic and structural plasticity within the reward circuitry [44, 45]. Some of the key molecular substrates underlying these changes in NAc have been identified, including alteration of growth factor and GTPase signaling and regulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor insertion and activity. Excitingly, many studies are now expanding on this work to investigate circuit-specific changes in molecular mechanisms that underlie synaptic and structural plasticity related to drug addiction. Here, we present highlights from a few recent studies pushing the field to incorporate a circuit-level understanding of molecular and functional changes underlying drug responses.

Brain-Derived Neurotrophic Factor

Neurotrophic factor signaling, and, in particular, that related to brain-derived neurotrophic factor (BDNF) action at the tropomyosin kinase B (TrkB) receptor, and its downstream effects, have been implicated in drug dependence and addiction [46]. Multiple studies find that BDNF expression is increased in response to both self- and investigator-administered cocaine throughout the reward circuitry, including in NAc, PFC, VTA, and amygdala [47–51]. However, the effect of increased BDNF expression or signaling on cocaine-related behaviors is region-specific [52]. For example, increasing BDNF in the NAc *versus* PFC produces opposite effects on cocaine intake. Increased BDNF in NAc leads to increased cocaine reward, locomotor activity, self-administration, and reinstatement behaviors, while decreasing BDNF expression or activity of the TrkB receptor decreases these same behaviors [47, 53–56]. Alternatively, in PFC increasing BDNF reduces cocaine seeking, while decreasing BDNF results in increased intake [57–60].

Given that changes in BDNF could also mediate structural and synaptic plasticity relevant to cocaine addiction through known actions modulating dendritic spine morphology and synaptic plasticity [46, 61], the question of whether BDNF could be a therapeutic target for cocaine addiction is dependent on whether competing changes within the reward circuit could abrogate benefits. Investigators have now begun to explore this possibility, as a recent paper described the use of a brain-penetrant TrkB antagonist [Tat-cyclotraxin-B (TC)] in rats undergoing long access or short access cocaine self-administration [62]. Systemic administration of TC decreased cocaine intake in both long access and short access rats, both during fixed ratio and progressive ratio testing, without affecting glucose/saccharin intake. Further, systemic administration of TC was also sufficient to reduce cocaine-induced reinstatement. Interestingly, TC normalized cocaine-induced changes in phospho-TrkB in both NAc and PFC, normalizing both the cocaine-induced increase in NAc and the cocaine-induced decrease in PFC. The mechanisms driving the brain-region specific changes in phospho-TrkB following cocaine self-administration remain unclear, as does the mechanism by which TC is able to reverse these changes in both brain regions, but this differential effect aligns with previous data showing opposite effects of decreased TrkB signaling in NAc and VTA and suggests that TrkB antagonism may be a viable option for treatment of cocaine addiction. Thus, future studies should assess not only changes in signaling in specific reward brain regions, but also the overall effect throughout the reward circuitry.

Small GTPase Signaling

Drugs of abuse also induce changes in neuronal structure, with one of the most-studied aspects being the change in number and structure of dendritic spines in NAc after cocaine exposure [44, 61, 63]. The maturation of dendritic spines from immature, thin spines to mature mushroom-shaped spines is associated with protein synthesis and receptor insertion (such as an increase in functional synaptic AMPA receptors) that corresponds to increased excitatory synaptic function [64]. In NAc, changes in MSN spine structure and synaptic strength vary as a function of time. Initially following cocaine exposure there is an increase in immature spines and decreased synaptic strength (see discussion of silent synapses below), while at longer time points postexposure (weeks to months), there is an increase in mature spines and synaptic strengthening [61, 65–67]. Importantly, these changes also correlate with behavior, as a similar early/late time course is observed in behavioral assays of cocaine seeking and reward [26, 67–69]. Given that dendritic spines are the prominent site for excitatory transmission, understanding circuit-specific changes in dendritic spine structure and function may yield important insight into altered circuit activity induced by cocaine exposure that may underlie addiction-related behaviors, such as relapse to drug seeking.

To this end, a recent study describes the role of the small GTPase Rap1b in cocaine-mediated dendritic remodeling in NAc, where Rap1b is elevated 24 h following cocaine exposure (administrator or self-administration) and is reduced 4 weeks later [70], analogous to the time course for spine changes. Further, NAc-specific knockout of Rap1b is sufficient to prevent cocaine induction of immature spines, and increasing Rap1b is sufficient to increase cocaine-driven locomotor activity and reward, suggesting it plays a key role in cocaine-induced changes in dendritic spine density and subsequent behavior. Critically, the authors then go on to explore which potential glutamatergic inputs are regulating these changes in spine density, and they find that optogenetic

stimulation of glutamatergic terminals from IL, but not vHIPP or BLA, increases Rap1b in NAc. Further, IL–NAc terminal stimulation was sufficient to induce a significant cocaine conditioned place preference (CPP) effect, and this was abolished in mice with knockdown of Rap1b in NAc. These data nicely align with earlier results showing an increase in immature synapses in the IL-NAc circuit immediately following cocaine self-administration (when Rap1b is increased), followed by synaptic maturation after prolonged withdrawal, producing an antirelapse effect [26], consistent with decreased Rap1b expression at the same time point. Importantly, in this study, there was also a circuit-specific effect, as remodeling of the PrL NAc *versus* IL NAc projections following prolonged abstinence yielded opposite effects, with PrL projections facilitating cocaine incubation/craving, and IL-NAc contributing to an antirelapse phenotype.

AMPA Receptor Function

This synaptic remodeling is not simply a change in the gross structure of the postsynaptic element (the spine), but also involves changes in the synaptic machinery that alter the function of the glutamatergic synapse [71]. For instance, immediately after prolonged exposure to cocaine, NAc MSNs exhibit an increase in the number of "silent synapses"—a signature of immature glutamatergic synapses that contain only NMDA receptors without stably expressed AMPA receptors [72]. However, after extended withdrawal from cocaine (ranging from 10 to 45 days), these synapses become "unsilenced" through synaptic insertion of AMPA receptors, including the Ca^{2+}-permeable GluA2-lacking variety, a process that directly correlates with the incubation of drug-seeking behavior, or increased "craving" [73].

Moreover, this effect appeared to be circuit-specific, as both the electrophysiological and behavioral outputs were directly linked to BLA inputs onto NAc MSNs [73, 74]. In parallel, another group investigated circuit-specific AMPA-dependent plasticity of vHIPP and mPFC inputs onto NAc MSNs in the context of 1 month of withdrawal from cocaine self-administration [31]. They found that cue-induced cocaine seeking at this time point correlated with reduced AMPA/NMDA ratio at mPFC inputs onto NAc D1 MSNs, while AMPA/NMDA ratio was increased at vHIPP inputs. Importantly, simultaneous reversal of these synaptic modifications at both inputs prevented cue-induced cocaine seeking, while selective reversal at mPFC inputs impaired response discrimination and selective reversal at vHIPP inputs reduced response vigor.

In combination, these studies demonstrate that plasticity of individual microcircuits may mediate specific aspects of drug-related behavior, but the entire reward circuitry is altered by chronic exposure to, and withdrawal from, addictive drugs, and these alterations likely drive drug craving and relapse [43, 73, 75]. Elucidation of common molecular mechanisms that facilitate drug-dependent remodeling of both specific reward microcircuits and general reward-related synapses remains a critical area of study, and a better understanding of functional outputs of these mechanisms will be critical for improved addiction treatment.

Optogenetic Dissection of Drug-Related Behaviors

VTA DA Stimulation

Optogenetic tools allow direct control of a defined subset of neurons (via genetic signature) in freely moving animals through the expression of light-activated channels that increase (channelrhodopsin, ChR2) or inhibit (archaerhodopsin; halorhodpsin) neuronal activity [76]. Optogenetic approaches have proven instrumental in identifying circuits necessary for various aspects of reward and addiction [77]. For example, early work confirmed the role for VTA DA neuron activity in reward-related behaviors, such that phasic optical stimulation of VTA DA neurons expressing channelrhodopsin was sufficient to produce CPP and increased DA release in the NAc [5]. Follow-up work demonstrated that optical activation of VTA DA neurons was also sufficient for development of positive reinforcement in a food-seeking operant task [78] and to support intracranial self-stimulation [6]. More recently, the role of VTA DA activity in reward behaviors more relevant to addiction, specifically compulsive use despite negative consequences, has been investigated using optogenetics [7]. In this study, mice were trained in an operant stimulation task in which an active lever press resulted in a burst stimulation of VTA DA neurons. Mice readily acquired the optogenetic self-stimulation behavior, and this reinforcement appeared to rely on the same circuits as drugs of abuse, as an injection of cocaine was capable of decreasing self-stimulation in a dose-dependent manner. In a further demonstration of the similarity between optogenetic self-stimulation and cocaine self-administration, mice exhibited similar cue-induced seeking behavior and changes in NAc synaptic plasticity (e.g., an increased AMPA/NMDA ratio in D1, but not D2, MSNs), following 30 days of abstinence from VTA DA self-stimulation, very similar to that observed following cocaine [31, 79]. Finally, in a subset of mice, VTA DA optical self-stimulation was sufficient to induce continued responding in the face of an electric foot shock punishment paired with the optical stimulation, similar to results observed for cocaine self-administration in rat studies [80], suggesting that VTA DA activity is sufficient to mediate the compulsive-like behavior in the face of adverse consequences associated with addiction. The authors went on to explore which brain regions might contribute to the phenotype of continuing to self-stimulate in the presence of punishment, and identified the orbitofrontal

cortex (OFC) as a critical mediator of this response: the OFC was activated specifically in mice resistant to punishment, OFC pyramidal neurons were more excitable in resistant mice compared with naïve and yoked controls, and silencing OFC neurons was sufficient to convert punishment resistant mice to susceptible. These studies highlight the facility of optogenetic approaches to confirm activity of specific neurons/brain regions in addictive behavior and use these approaches to model addictive behavior itself, in the absence of drugs, to identify common underlying mechanisms.

NAc MSN Stimulation

While the activity of VTA DA neurons is critical to drive initial reward-related drug seeking, a critical nexus for the progression to addiction is thought to occur in NAc, where the reward-related information (DA) modulates glutamatergic inputs from cortical and limbic regions to produce behavior. As discussed above, the predominant neurons in NAc are MSNs, and considerable effort has been put forth to understand the changes in function induced by drugs of abuse in D1 *versus* D2 MSNs. While the use of D1- and D2-selective agonists and antagonists has been instrumental in defining the often opposing effects of these 2 subclasses of neurons, optogenetic tools offer a mechanism to investigate changes in the activity of these neurons, and their connections, in real time. For example, early optogenetic work found that in contrast to VTA DA neuron optical activation, D1 or D2 MSN activation did not generate place preference [81]. However, activation of D1 MSNs during cocaine exposure was sufficient to induce CPP to a subthreshold dose of cocaine, while D2 MSN activation produced the opposite result, decreasing CPP when administered during training. While both D1 and D2 MSNs receive dopaminergic and glutamatergic input from similar structures (e.g., VTA, BLA, mPFC, vHIPP, midline nuclei of the thalamus), the cocaine-induced changes in synaptic plasticity can be cell type-specific, as are their outputs, which likely contribute to their differential effects on cocaine-related behavior [19]. This has recently been shown to be the case in the VP, a robust target of both D1 and D2 NAc MSNs, where cocaine exposure simultaneously potentiated D1 NAc–VP output, but depressed D2 NAc–VP output [82]. Further, these plasticity changes mediated distinct aspects of addictive-like behaviors. Restoration of function at D1 NAc–VP synapses eliminated cocaine locomotor sensitization, while rescue at D2 NAc–VP synapses reversed cocaine withdrawal-induced anhedonia, suggesting that NAc D1 *versus* D2 MSN efferents to VP regulate distinct behavioral states [82]. This work highlights not only the differential impact of D1 *versus* D2 MSN circuits, but also the importance of the NAc–VP circuit in cocaine-related behaviors, a topic of great recent interest [83–87].

PFC–NAc Stimulation

There is also evidence that glutamatergic afferents to the NAc differentially support reward behavior. For example, optogenetic stimulation of NAc axonal terminals originating from BLA neurons was sufficient to promote self-stimulation, indicative of reward, while simulation of terminals originating from mPFC neurons was not [34]. Moreover, work from numerous groups suggests that the PFC–NAc glutamatergic circuit is remodeled in rodent models of addiction, and that these changes play an integral role in drug-seeking behavior following forced abstinence or extinction from chronic cocaine. However, the role of the mPFC is complicated, as effects differ between mPFC subregions. In general, evidence suggests that activation of PrL–NAc projections is important for reinstatement behavior following cocaine extinction [88–90], while *in*activation of IL–NAc reinstates seeking behavior following extinction [91, 92]. Similar results were recently observed following forced withdrawal in the cocaine incubation paradigm [54, 79]. While similar neuroplasticity (maturation of silent synapses) was induced in both the PrL–NAc and IL–NAc circuits, optogenetic reversal of the plasticity produced opposite behavioral effects within each circuit, as the IL–NAc reversal led to increased incubation of cocaine craving and PrL–NAc reversal inhibited incubation [26].

Indeed, while it is clear that glutamatergic regulation of NAc is critical for various aspects of addiction, including drug seeking and relapse, the roles of specific inputs are complex. Results differ between the region of PFC examined (PrL, IL, or orbitofrontal), the cocaine-related paradigm and time point examined (reinstatement, resistance to punishment, seeking, or escalation), the stimulation parameters, and the species examined [27, 93]. Thus, though current results present a complex and cloudy picture of the molecular mechanisms of circuit-specific brain alterations underlying addiction, the tools for clarifying and integrating these results are becoming available, and a clearer understanding of these mechanisms will be a critical step for uncovering circuit-specific therapies for addiction.

Circuit-Based Therapeutics for Addiction

While considerable headway has been made in isolating the activity of specific neural circuits in aspects of addictive behavior using preclinical models, the translation of this knowledge to improve the diagnosis and treatment of addiction in humans lags behind. The solution to this problem rests, at least in part, in defining the effects of drug addiction on the human reward circuitry using imaging approaches. Much work has been done in this area, with many reports of drug-induced changes in both structure and function of regions within in the reward circuitry and many excellent reviews summarizing

this work [94, 95]. In this section, we will specifically focus on PFC and striatum (dorsal and ventral) and the connections between them, as these have offered the primary targets for approaches to alter human circuit function in the treatment of addiction.

In aggregate, current work suggests that PFC activity is decreased in drug abusers, with specific PFC subregions, including the dorsolateral PFC (dlPFC), mPFC, and OFC being of particular interest. Within these regions, there is evidence of both structural (e.g., decreased gray matter volume or cortical thickness) and functional (e.g., positron emission tomography, functional magnetic resonance imaging, and blood-oxygen level-dependent (BOLD) activity) abnormalities in cocaine abusers [94]. Alterations in the structure and function of these subregions are thought to contribute to changes in limbic arousal, executive function, and reward valuation that then contribute to behaviors such as craving, risk taking, and outcome prediction errors that underlie addiction and relapse. Moreover, altered activity within PFC subregions contributes to altered activity in the dorsal (caudate nucleus and putamen) and ventral (NAc) striatum. Changes in dorsal striatal activity are most associated with changes in movement, cognitive processing and habit formation, and stronger connectivity to the dlPFC. In contrast, the ventral striatum is more highly connected to the mPFC and OFC, and changes in activity in this region are more relevant to limbic control, and arousal states such as craving and "high".

Repetitive Transcranial Magnetic Stimulation for Treatment of Addiction

Research has also begun to translate findings from optogenetic studies in rodent models and apply them to human addicts. One strategy is to use repetitive transcranial magnetic stimulation (rTMS), as this is a noninvasive approach to alter neuronal activity that has been applied with success to other neuropsychiatric disorders such as depression [96]. Clinical trials using rTMS for addiction are ongoing, with studies investigating whether rTMS treatment is capable of decreasing craving for, or use of, multiple drugs of abuse, including alcohol, cocaine, methamphetamine, and tobacco [97]. Most studies to date have employed high-frequency rTMS (10–20 Hz) in the dlPFC in order to increase neuronal excitability and cortical activity [98, 99], as work from animal studies has shown that activity in PrL (the homologous PFC region in rodents) is decreased by chronic cocaine use, and optogenetic stimulation of PrL inhibits compulsive cocaine seeking [80]. Thus, rTMS of dlPFC in addicted individuals is expected to increase cortical activity and improve cognitive/executive control.

Two recent pilot studies have examined the effect of dlPFC rTMS on cocaine use in cocaine-addicted patients. The first compared unilateral rTMS treatment of cocaine-addicted patients with a pharmacological control group, to offset potential depressive-, anxiety-, and sleep-related symptoms often experienced when cocaine addicts stop using cocaine [100]. The rTMS group had a significantly reduced relapse rate (all drug urine screens were negative during initial 4-week treatment stage) compared with the control group. Moreover, in the second stage of the study, the pharmacological control group was given the option to receive rTMS treatment, which resulted in a significantly reduced relapse rate in this group as well (within-group comparison) that was indistinguishable from the relapse rate of patients receiving rTMS in stage 1. The improvement in relapse rate was mirrored by decreased drug craving in the rTMS group. A second study examined the effect on cocaine intake of bilateral PFC rTMS treatment of cocaine-addicted patients [101]. In contrast to the previous study, no differences in cocaine intake were observed between rTMS and control (sham stimulation) groups immediately following 4 weeks of treatment. However, there was a significant time effect, as the rTMS group showed a trend for decreased cocaine intake 3 to 6 months following treatment. There were multiple differences in the design of these 2 studies, which may have contributed to the results, including the rTMS protocol (unilateral *vs* bilateral), control comparison (pharmacological *vs* sham stimulus), and drug screen (urine *vs* hair analysis), that were likely amplified by the small sample sizes (32 and 18 patients, respectively).

While both of these studies involved a small number of individuals, the results are promising and suggest that rTMS can be safely used in cocaine-addicted patients. Further refinement of TMS approaches may offer a novel treatment for cocaine addiction, a critical advance given the lack of currently approved treatments. This includes the use of rTMS in other regions, such as mPFC. In this case, low-frequency stimulation would be used to decrease cortical activity in order to normalize the increased activity induced by drugs of abuse [102]. Promising pilot data find that long-term depression (LTD) -like continuous theta burst stimulation decreased cocaine craving in cocaine-dependent patients and decreased activity both in PFC and in projection regions such as the ventral striatum (via BOLD) immediately following a single rTMS stimulation compared with nonstimulated controls. While early results are encouraging, there are issues surrounding TMS use that could ultimately limit its effectiveness in the treatment of addiction including constraints on the specificity of stimulation target region, the frequency of treatments necessary, and the long-term persistence of any beneficial effects.

Deep Brain Stimulation for Treatment of Addiction

Another strategy proposed to translate the circuit-based findings of preclinical models to human addiction is the use of deep brain stimulation (DBS) [71]. DBS is the electrical stimulation of discrete brain regions through surgical implantation of current passing electrodes. While pioneered for the

treatment of Parkinson's disease, DBS has been employed more recently in the treatment of psychiatric disorders such as depression [103]. However, DBS does not offer the selectivity of preclinical optogenetic approaches, where activity of specific cells or projections within a region can be modulated, and this specificity may be critical in regions such as NAc, where general stimulation could prove ineffective owing to competing actions of multiple forms of plasticity (DA *vs* glutamate or input projection-specific effects). While general DBS approaches have been used with some success in preclinical animal models [104–106], recent work has attempted to refine the specificity of DBS by designing a protocol to reverse specific forms of plasticity induced by drugs of abuse in combination with the use of a pharmacological adjuvant that helps to eliminate opposing effects from the general stimulation [107]. Termed optically inspired DBS, a stimulation protocol was developed to induce LTD of excitatory synapses in the NAc in order to reverse cocaine-induced changes in neuroplasticity. This stimulation was then combined with administration of D1 receptor antagonist to block competing effects of the stimulation on DA release, thereby "unmasking" the desired glutamatergic plasticity. Critically, this approach was sufficient to both reverse the cocaine-induced changes in synaptic plasticity and cocaine locomotor sensitization. This study serves as an intriguing example of an approach to integrate the hard-earned knowledge of specific molecular and synaptic adaptations induced by drugs of abuse identified in animal models and apply them to improve treatment of addiction. Given that pilot studies in the use of DBS to treat addiction have now begun for alcohol, cocaine, and heroin addiction with some promising initial results [108–110], the implementation of drug-reward circuitry knowledge to affect therapeutic potential may have the field poised for a breakthrough.

Conclusions and Future Directions

In summary, our understanding of the circuitry underlying drug-related behaviors has increased greatly in recent years, driven by the development and implementation of opto- and chemogenetic approaches. Excitingly, these circuit-based approaches are now being used to explore the molecular mechanisms responsible for changes in drug-evoked structural and synaptic plasticity that underlie the maladaptive behavior. While these genetics-based studies have allowed for elegant dissection and elucidation of specific microcircuits relevant to various aspects of addiction, the challenge will be in integrating the findings from these distinct microcircuits back into a general model of addiction, given the complexity and interconnectedness of the brain-reward circuitry they have already revealed. Additionally, while many of the drug-evoked synaptic and structural plasticity changes described here are shared between different classes of abused drugs, others appear to be drug-class selective [46, 111, 112], which could present additional complexity in designing translational studies. However, the groundwork for a circuit model of addiction has been laid, and the insights gained from preclinical studies have started to be translated to the clinic. Alteration of reward circuit activity through rTMS and DBS offers a promising new avenue for treatment of addiction, and is a welcome advance given the lack of effective treatments for this devastating disorder.

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References

1. Swanson LW. The projections of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Res Bull 1982; 9: 321-353.
2. Nair-Roberts RG, Chatelain-Badie SD, Benson E, White-Cooper H, Bolam JP, Ungless MA. Stereological estimates of dopaminergic, GABAergic and glutamatergic neurons in the ventral tegmental area, substantia nigra and retrorubral field in the rat. Neuroscience 2008; 152:1024-1031.
3. Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A 1988; 85: 5274-5278.
4. Anderson SM, Pierce RC. Cocaine-induced alterations in dopamine receptor signaling: implications for reinforcement and reinstatement. Pharmacol Ther 2005; 106:389-403.
5. Tsai HC, Zhang F, Adamantidis A, et al. Phasic firing in dopaminergic neurons is sufficient for behavioral conditioning. Science 2009; 324:1080-1084.
6. Witten IB, Steinberg EE, Lee SY, et al. Recombinase-driver rat lines: tools, techniques, and optogenetic application to dopamine-mediated reinforcement. Neuron 2011; 72:721-733.
7. Pascoli V, Terrier J, Hiver A, Luscher C. Sufficiency of mesolimbic dopamine neuron stimulation for the progression to addiction. Neuron 2015; 88:1054-1066.
8. Lammel S, Lim BK, Malenka RC. Reward and aversion in a heterogeneous midbrain dopamine system. Neuropharmacology 2014; 76 Pt B:351-359.
9. Lammel S, Hetzel A, Hackel O, Jones I, Liss B, Roeper J. Unique properties of mesoprefrontal neurons within a dual mesocorticolimbic dopamine system. Neuron 2008; 57:760-773.
10. Lammel S, Ion DI, Roeper J, Malenka RC. Projection-specific modulation of dopamine neuron synapses by aversive and rewarding stimuli. Neuron 2011; 70:855-862.
11. Lammel S, Lim BK, Ran C, et al. Input-specific control of reward and aversion in the ventral tegmental area. Nature 2012; 491:212-217.
12. Nectow AR, Ekstrand MI, Friedman JM. Molecular characterization of neuronal cell types based on patterns of projection with Retro-TRAP. Nat Protoc 2015; 10:1319-1327.

13. Ekstrand MI, Nectow AR, Knight ZA, Latcha KN, Pomeranz LE, Friedman JM. Molecular profiling of neurons based on connectivity. Cell 2014; 157:1230-1242.
14. van Zessen R, Phillips JL, Budygin EA, Stuber GD. Activation of VTA GABA neurons disrupts reward consumption. Neuron 2012; 73:1184-1194.
15. Tan KR, Yvon C, Turiault M, et al. GABA neurons of the VTA drive conditioned place aversion. Neuron 2012; 73:1173-1183.
16. Gerfen CR, Engber TM, Mahan LC, et al. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science 1990; 250:1429-1432.
17. Gerfen CR, Surmeier DJ. Modulation of striatal projection systems by dopamine. Annu Rev Neurosci 2011; 34:441-466.
18. Kupchik YM, Brown RM, Heinsbroek JA, Lobo MK, Schwartz DJ, Kalivas PW. Coding the direct/indirect pathways by D1 and D2 receptors is not valid for accumbens projections. Nat Neurosci 2015; 18:1230-1232.
19. Smith RJ, Lobo MK, Spencer S, Kalivas PW. Cocaine-induced adaptations in D1 and D2 accumbens projection neurons (a dichotomy not necessarily synonymous with direct and indirect pathways). Curr Opin Neurobiol 2013; 23:546-552.
20. Lenz JD, Lobo MK. Optogenetic insights into striatal function and behavior. Behav Brain Res 2013; 255:44-54.
21. Saddoris MP, Sugam JA, Cacciapaglia F, Carelli RM. Rapid dopamine dynamics in the accumbens core and shell: learning and action. Front Biosci (Elite Ed) 2013; 5:273-288.
22. Meredith GE, Baldo BA, Andrezjewski ME, Kelley AE. The structural basis for mapping behavior onto the ventral striatum and its subdivisions. Brain Struct Funct 2008; 213:17-27.
23. Sesack SR, Grace AA. Cortico-basal ganglia reward network: microcircuitry. Neuropsychopharmacology 2010; 35:27-47.
24. Floresco SB. The nucleus accumbens: an interface between cognition, emotion, and action. Annu Rev Psychol 2015; 66:25-52.
25. Kalivas PW, Volkow N, Seamans J. Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. Neuron 2005; 45:647-650.
26. Ma YY, Lee BR, Wang X, et al. Bidirectional modulation of incubation of cocaine craving by silent synapse-based remodeling of prefrontal cortex to accumbens projections. Neuron 2014; 83: 1453-1467.
27. Scofield MD, Heinsbroek JA, Gipson CD, et al. The nucleus accumbens: mechanisms of addiction across drug classes reflect the importance of glutamate homeostasis. Pharmacol Rev 2016; 68: 816-871.
28. Oleskevich S, Descarries L, Lacaille JC. Quantified distribution of the noradrenaline innervation in the hippocampus of adult rat. J Neurosci 1989; 9:3803-3815.
29. French SJ, Totterdell S. Individual nucleus accumbens-projection neurons receive both basolateral amygdala and ventral subicular afferents in rats. Neuroscience 2003; 119:19-31.
30. French SJ, Hailstone JC, Totterdell S. Basolateral amygdala efferents to the ventral subiculum preferentially innervate pyramidal cell dendritic spines. Brain Res 2003; 981:160-167.
31. Pascoli V, Terrier J, Espallergues J, Valjent E, O'Connor EC, Luscher C. Contrasting forms of cocaine-evoked plasticity control components of relapse. Nature 2014; 509:459-464.
32. Vezina P, Giovino AA, Wise RA, Stewart J. Environment-specific cross-sensitization between the locomotor activating effects of morphine and amphetamine. Pharmacol Biochem Behav 1989; 32:581-584.
33. Charara A, Grace AA. Dopamine receptor subtypes selectively modulate excitatory afferents from the hippocampus and amygdala to rat nucleus accumbens neurons. Neuropsychopharmacology 2003; 28:1412-1421.
34. Stuber GD, Sparta DR, Stamatakis AM, et al. Excitatory transmission from the amygdala to nucleus accumbens facilitates reward seeking. Nature 2011; 475:377-380.
35. Ambroggi F, Ishikawa A, Fields HL, Nicola SM. Basolateral amygdala neurons facilitate reward-seeking behavior by exciting nucleus accumbens neurons. Neuron 2008; 59:648-661.
36. Janak PH, Tye KM. From circuits to behaviour in the amygdala. Nature 2015; 517:284-292.
37. Zhu Y, Wienecke CF, Nachtrab G, Chen X. A thalamic input to the nucleus accumbens mediates opiate dependence. Nature 2016; 530:219-222.
38. Browning JR, Jansen HT, Sorg BA. Inactivation of the paraventricular thalamus abolishes the expression of cocaine conditioned place preference in rats. Drug Alcohol Depend 2014; 134:387-390.
39. James MH, Charnley JL, Flynn JR, Smith DW, Dayas CV. Propensity to 'relapse' following exposure to cocaine cues is associated with the recruitment of specific thalamic and epithalamic nuclei. Neuroscience 2011; 199:235-242.
40. James MH, Charnley JL, Jones E, et al. Cocaine- and amphetamine-regulated transcript (CART) signaling within the paraventricular thalamus modulates cocaine-seeking behaviour. PLOS ONE 2010; 5:e12980.
41. Joffe ME, Grueter BA. Cocaine experience enhances thalamoaccumbens N-methyl-D-aspartate receptor function. Biol Psychiatry 2016; 80:671-681.
42. Neumann PA, Wang Y, Yan Y, et al. Cocaine-induced synaptic alterations in thalamus to nucleus accumbens projection. Neuropsychopharmacology 2016; 41:2399-2410.
43. Luscher C. The emergence of a circuit model for addiction. Annu Rev Neurosci 2016; 39:257-276.
44. Golden SA, Russo SJ. Mechanisms of psychostimulant-induced structural plasticity. Cold Spring Harb Perspect Med 2012; 2.
45. Luscher C, Malenka RC. Drug-evoked synaptic plasticity in addiction: from molecular changes to circuit remodeling. Neuron 2011; 69:650-663.
46. Russo SJ, Mazei-Robison MS, Ables JL, Nestler EJ. Neurotrophic factors and structural plasticity in addiction. Neuropharmacology 2009; 56(Suppl. 1):73-82.
47. Graham DL, Edwards S, Bachtell RK, DiLeone RJ, Rios M, Self DW. Dynamic BDNF activity in nucleus accumbens with cocaine use increases self-administration and relapse. Nat Neurosci 2007; 10:1029-1037.
48. Graham DL, Krishnan V, Larson EB, et al. Tropomyosin-related kinase B in the mesolimbic dopamine system: region-specific effects on cocaine reward. Biol Psychiatry 2009; 65:696-701.
49. Grimm JW, Lu L, Hayashi T, Hope BT, Su TP, Shaham Y. Time-dependent increases in brain-derived neurotrophic factor protein levels within the mesolimbic dopamine system after withdrawal from cocaine: implications for incubation of cocaine craving. J Neurosci 2003; 23:742-747.
50. Le Foll B, Diaz J, Sokoloff P. A single cocaine exposure increases BDNF and D3 receptor expression: implications for drug-conditioning. Neuroreport 2005; 16:175-178.
51. Fumagalli F, Moro F, Caffino L, et al. Region-specific effects on BDNF expression after contingent or non-contingent cocaine i.v. self-administration in rats. Int J Neuropsychopharmacol 2013; 16: 913-918.
52. McGinty JF, Whitfield TW, Jr., Berglind WJ. Brain-derived neurotrophic factor and cocaine addiction. Brain Res 2010; 1314:183-193.
53. Horger BA, Iyasere CA, Berhow MT, Messer CJ, Nestler EJ, Taylor JR. Enhancement of locomotor activity and conditioned reward to cocaine by brain-derived neurotrophic factor. J Neurosci 1999; 19:4110-4122.

54. Lu L, Grimm JW, Hope BT, Shaham Y. Incubation of cocaine craving after withdrawal: a review of preclinical data. Neuropharmacology 2004; 47(Suppl. 1):214-226.
55. Li X, DeJoseph MR, Urban JH, et al. Different roles of BDNF in nucleus accumbens core versus shell during the incubation of cue-induced cocaine craving and its long-term maintenance. J Neurosci 2013; 33:1130-1142.
56. Bahi A, Boyer F, Chandrasekar V, Dreyer JL. Role of accumbens BDNF and TrkB in cocaine-induced psychomotor sensitization, conditioned-place preference, and reinstatement in rats. Psychopharmacology (Berl) 2008; 199:169-182.
57. Whitfield TW, Jr., Shi X, Sun WL, McGinty JF. The suppressive effect of an intra-prefrontal cortical infusion of BDNF on cocaine-seeking is Trk receptor and extracellular signal-regulated protein kinase mitogen-activated protein kinase dependent. J Neurosci 2011; 31:834-842.
58. Berglind WJ, See RE, Fuchs RA, et al. A BDNF infusion into the medial prefrontal cortex suppresses cocaine seeking in rats. Eur J Neurosci 2007; 26:757-766.
59. Berglind WJ, Whitfield TW, Jr., LaLumiere RT, Kalivas PW, McGinty JF. A single intra-PFC infusion of BDNF prevents cocaine-induced alterations in extracellular glutamate within the nucleus accumbens. J Neurosci 2009; 29:3715-3719.
60. Sadri-Vakili G, Kumaresan V, Schmidt HD, et al. Cocaine-induced chromatin remodeling increases brain-derived neurotrophic factor transcription in the rat medial prefrontal cortex, which alters the reinforcing efficacy of cocaine. J Neurosci 2010; 30:11735-11744.
61. Russo SJ, Dietz DM, Dumitriu D, Morrison JH, Malenka RC, Nestler EJ. The addicted synapse: mechanisms of synaptic and structural plasticity in nucleus accumbens. Trends Neurosci 2010; 33:267-276.
62. Verheij MM, Vendruscolo LF, Caffino L, et al. Systemic delivery of a brain-penetrant TrkB antagonist reduces cocaine self-administration and normalizes TrkB signaling in the nucleus accumbens and prefrontal cortex. J Neurosci 2016; 36:8149-8159.
63. Dietz DM, Dietz KC, Nestler EJ, Russo SJ. Molecular mechanisms of psychostimulant-induced structural plasticity. Pharmacopsychiatry 2009; 42(Suppl. 1):S69-78.
64. Tada T, Sheng M. Molecular mechanisms of dendritic spine morphogenesis. Curr Opin Neurobiol 2006; 16:95-101.
65. Dong Y, Nestler EJ. The neural rejuvenation hypothesis of cocaine addiction. Trends Pharmacol Sci 2014; 35:374-383.
66. Shen HW, Toda S, Moussawi K, Bouknight A, Zahm DS, Kalivas PW. Altered dendritic spine plasticity in cocaine-withdrawn rats. J Neurosci 2009; 29:2876-2884.
67. Dietz DM, Sun H, Lobo MK, et al. Rac1 is essential in cocaine-induced structural plasticity of nucleus accumbens neurons. Nat Neurosci 2012; 15:891-896.
68. Pascoli V, Turiault M, Luscher C. Reversal of cocaine-evoked synaptic potentiation resets drug-induced adaptive behaviour. Nature 2011; 481:71-75.
69. Gipson CD, Kupchik YM, Shen H, Reissner KJ, Thomas CA, Kalivas PW. Relapse induced by cues predicting cocaine depends on rapid, transient synaptic potentiation. Neuron. 2013; 77:867-872.
70. Cahill ME, Bagot RC, Gancarz AM, et al. Bidirectional synaptic structural plasticity after chronic cocaine administration occurs through Rap1 small GTPase signaling. Neuron 2016; 89:566-582.
71. Luscher C, Pascoli V, Creed M. Optogenetic dissection of neural circuitry: from synaptic causalities to blue prints for novel treatments of behavioral diseases. Curr Opin Neurobiol 2015; 35:95-100.
72. Huang YH, Lin Y, Mu P, et al. In vivo cocaine experience generates silent synapses. Neuron 2009; 63:40-47.
73. Huang YH, Schluter OM, Dong Y. Silent synapses speak up: updates of the neural rejuvenation hypothesis of drug addiction. Neuroscientist 2015; 21:451-459.
74. Lee BR, Ma YY, Huang YH, et al. Maturation of silent synapses in amygdala-accumbens projection contributes to incubation of cocaine craving. Nat Neurosci 2013; 16:1644-1651.
75. Volkow ND, Morales M. The brain on drugs: from reward to addiction. Cell 2015; 162:712-725.
76. Deisseroth K. Optogenetics. Nat Methods 2011; 8:26-29.
77. Stuber GD, Britt JP, Bonci A. Optogenetic modulation of neural circuits that underlie reward seeking. Biol Psychiatry 2012; 71:1061-1067.
78. Adamantidis AR, Tsai HC, Boutrel B, et al. Optogenetic interrogation of dopaminergic modulation of the multiple phases of reward-seeking behavior. J Neurosci 2011; 31:10829-10835.
79. Wolf ME. Synaptic mechanisms underlying persistent cocaine craving. Nat Rev Neurosci 2016; 17:351-365.
80. Chen BT, Yau HJ, Hatch C, et al. Rescuing cocaine-induced prefrontal cortex hypoactivity prevents compulsive cocaine seeking. Nature 2013; 496:359-362.
81. Lobo MK, Covington HE, 3rd, Chaudhury D, et al. Cell type-specific loss of BDNF signaling mimics optogenetic control of cocaine reward. Science 2010; 330:385-390.
82. Creed M, Ntamati NR, Chandra R, Lobo MK, Luscher C. Convergence of reinforcing and anhedonic cocaine effects in the ventral pallidum. Neuron 2016; 92:214-226.
83. Heinsbroek JA, Neuhofer DN, Griffin WC, 3rd, et al. Loss of plasticity in the D2-accumbens pallidal pathway promotes cocaine seeking. J Neurosci 2017; 37:757-767.
84. Wang L, Shen M, Yu Y, et al. Optogenetic activation of GABAergic neurons in the nucleus accumbens decreases the activity of the ventral pallidum and the expression of cocaine-context-associated memory. Int J Neuropsychopharmacol 2014; 17:753-763.
85. James MH, Aston-Jones G. The ventral pallidum: proposed integrator of positive and negative factors in cocaine abuse. Neuron 2016; 92:5-8.
86. Stefanik MT, Kupchik YM, Brown RM, Kalivas PW. Optogenetic evidence that pallidal projections, not nigral projections, from the nucleus accumbens core are necessary for reinstating cocaine seeking. J Neurosci 2013; 33:13654-13662.
87. Root DH, Melendez RI, Zaborszky L, Napier TC. The ventral pallidum: subregion-specific functional anatomy and roles in motivated behaviors. Prog Neurobiol 2015; 130:29-70.
88. Kalivas PW, McFarland K. Brain circuitry and the reinstatement of cocaine-seeking behavior. Psychopharmacology (Berl) 2003; 168:44-56.
89. Kalivas PW. The glutamate homeostasis hypothesis of addiction. Nat Rev Neurosci 2009; 10:561-572.
90. McGlinchey EM, James MH, Mahler SV, Pantazis C, Aston-Jones G. Prelimbic to accumbens core pathway is recruited in a dopamine-dependent manner to drive cued reinstatement of cocaine seeking. J Neurosci 2016; 36:8700-8711.
91. LaLumiere RT, Smith KC, Kalivas PW. Neural circuit competition in cocaine-seeking: roles of the infralimbic cortex and nucleus accumbens shell. Eur J Neurosci 2012; 35:614-622.
92. Peters J, LaLumiere RT, Kalivas PW. Infralimbic prefrontal cortex is responsible for inhibiting cocaine seeking in extinguished rats. J Neurosci 2008; 28:6046-6053.
93. Moorman DE, James MH, McGlinchey EM, Aston-Jones G. Differential roles of medial prefrontal subregions in the regulation of drug seeking. Brain Res 2015; 1628:130-146.
94. Hanlon CA, Dowdle LT, Jones JL. Biomarkers for success: using neuroimaging to predict relapse and develop brain stimulation treatments for cocaine-dependent individuals. Int Rev Neurobiol 2016; 129:125-156.

95. Volkow ND, Wang GJ, Fowler JS, Tomasi D. Addiction circuitry in the human brain. Annu Rev Pharmacol Toxicol 2012; 52:321-336.
96. Janicak PG, Dokucu ME. Transcranial magnetic stimulation for the treatment of major depression. Neuropsychiatr Dis Treat 2015; 11:1549-1560.
97. Gorelick DA, Zangen A, George MS. Transcranial magnetic stimulation in the treatment of substance addiction. Ann N Y Acad Sci 2014; 1327:79-93.
98. Speer AM, Kimbrell TA, Wassermann EM, et al. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. Biol Psychiatry 2000; 48:1133-1141.
99. Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. Clin Neurophysiol 2006; 117:2584-2596.
100. Terraneo A, Leggio L, Saladini M, Ermani M, Bonci A, Gallimberti L. Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: A pilot study. Eur Neuropsychopharmacol 2016; 26:37-44.
101. Bolloni C, Panella R, Pedetti M, et al. Bilateral transcranial magnetic stimulation of the prefrontal cortex reduces cocaine intake: a pilot study. Front Psychiatry 2016; 7:133.
102. Hanlon CA, Dowdle LT, Austelle CW, et al. What goes up, can come down: Novel brain stimulation paradigms may attenuate craving and craving-related neural circuitry in substance dependent individuals. Brain Res 2015; 1628:199-209.
103. Holtzheimer PE, Mayberg HS. Deep brain stimulation for psychiatric disorders. Annu Rev Neurosci 2011; 34:289-307.
104. Pierce RC, Vassoler FM. Deep brain stimulation for the treatment of addiction: basic and clinical studies and potential mechanisms of action. Psychopharmacology (Berl) 2013; 229:487-491.
105. Vassoler FM, Schmidt HD, Gerard ME, et al. Deep brain stimulation of the nucleus accumbens shell attenuates cocaine priming-induced reinstatement of drug seeking in rats. J Neurosci 2008; 28: 8735-8739.
106. Vassoler FM, White SL, Hopkins TJ, et al. Deep brain stimulation of the nucleus accumbens shell attenuates cocaine reinstatement through local and antidromic activation. J Neurosci 2013; 33: 14446-14454.
107. Creed M, Pascoli VJ, Luscher C. Addiction therapy. Refining deep brain stimulation to emulate optogenetic treatment of synaptic pathology. Science 2015; 347:659-664.
108. Muller UJ, Sturm V, Voges J, et al. Nucleus accumbens deep brain stimulation for alcohol addiction—safety and clinical long-term results of a pilot trial. Pharmacopsychiatry 2016; 49:170-173.
109. Kuhn J, Moller M, Treppmann JF, et al. Deep brain stimulation of the nucleus accumbens and its usefulness in severe opioid addiction. Mol Psychiatry 2014; 19:145-146.
110. Goncalves-Ferreira A, do Couto FS, Rainha Campos A, Lucas Neto LP, Goncalves-Ferreira D, Teixeira J. Deep brain stimulation for refractory cocaine dependence. Biol Psychiatry 2016; 79:e87-e89.
111. Graziane NM, Sun S, Wright WJ, et al. Opposing mechanisms mediate morphine- and cocaine-induced generation of silent synapses. Nat Neurosci 2016; 19:915-925.
112. Koo JW, Mazei-Robison MS, Chaudhury D, et al. BDNF is a negative modulator of morphine action. Science 2012; 338:124-128.