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THE NEUROSCIENCE OF DRUG REWARD AND ADDICTION

Nora D. Volkow, Michael Michaelides, and Ruben Baler

National Institute on Drug Abuse, National Institutes of Health, Bethesda, Maryland

Volkow ND, Michaelides M, Baler R. The Neuroscience of Drug Reward and Addiction. *Physiol Rev* 99: 2115–2140, 2019. Published September 11, 2019; doi:10.1152/physrev.00014.2018.—Drug consumption is driven by a drug's pharmacological effects, which are experienced as rewarding, and is influenced by genetic, developmental, and psychosocial factors that mediate drug accessibility, norms, and social support systems or lack thereof. The reinforcing effects of drugs mostly depend on dopamine signaling in the nucleus accumbens, and chronic drug exposure triggers glutamatergic-mediated neuroadaptations in dopamine striato-thalamo-cortical (predominantly in prefrontal cortical regions including orbitofrontal cortex and anterior cingulate cortex) and limbic pathways (amygdala and hippocampus) that, in vulnerable individuals, can result in addiction. In parallel, changes in the extended amygdala result in negative emotional states that perpetuate drug taking as an attempt to temporarily alleviate them. Counterintuitively, in the addicted person, the actual drug consumption is associated with an attenuated dopamine increase in brain reward regions, which might contribute to drug-taking behavior to compensate for the difference between the magnitude of the expected reward triggered by the conditioning to drug cues and the actual experience of it. Combined, these effects result in an enhanced motivation to "seek the drug" (energized by dopamine increases triggered by drug cues) and an impaired prefrontal top-down self-regulation that favors compulsive drug-taking against the backdrop of negative emotionality and an enhanced interoceptive awareness of "drug hunger." Treatment interventions intended to reverse these neuroadaptations show promise as therapeutic approaches for addiction.

cannabis; dopamine; glutamate; nucleus accumbens; opioids; substance use disorders

Neuroscience research has revealed that addiction is a chronic, relapsing disease of the brain triggered by repeated exposure to drugs in those who are vulnerable because of genetics and developmental or adverse social exposures. As a result, the reward circuit's capacity to respond to reward and motivate actions that are not drug related is decreased, the sensitivity of the emotional circuits to stress is enhanced, and the capacity to self-regulate is impaired. The result is compulsive drug seeking and drug taking despite severe harms and an inability to control the strong urges to consume the drug, even when there is a strong desire to quit. The changes in the brain responsible for these maladaptive behaviors can persist for months or even years after drug discontinuation but are amenable to treatment. Treatment should be aimed at improving self-regulation; helping to control craving and the emergence of distressing emotions, including depression and anxiety; and improving the sensitivity to alternative reinforcers. Addiction is a chronic disease, so its treatment should follow a sustained model of intervention, the intensity of which should be adjusted to the stage of the disease. Treatment should also be personalized and calibrated to the severity of the addiction, the presence of comorbidities, and the individual's support systems. Crucially, addiction can be prevented, and both universal as well as tailored strategies can significantly reduce substance use disorder in the individual and in a population.

I. INTRODUCTION

There is an inherent need in all sentient beings to seek out positive and avoid negative stimuli, a universal formula that has evolved to maximize adaptive fitness and the chances of survival. The extent to which strategies for attaining or avoiding such stimuli are successful depends on complex interactions between an organism and its environment that are orchestrated by the nervous system. Neurobiology employs processes refined during evolution, such as homeostasis, sensory perception, associative and nonassociative learning, emotions, and decision-making, to shape an organism's response to environmental stimuli and to maximize its ability to harness their predictable features and to adapt to unpredictable ones. Although types of stimuli vary from one species to another, there are striking similarities among different species,

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in their responses to positive (e.g., food and sex) and negative (e.g., pain and environmental threats) stimuli. This common representation, which reflects the critical role of such stimuli in boosting the odds of survival, is often reflected at the neurobiological level, whereby different species tap into similar brain structural, neurochemical, and functional strategies to tackle similar problems (77, 284).

Ingenuity has enabled humans to extract and refine highly reinforcing stimuli against which naturally occurring reinforcers cannot easily compete. The most notable example is our ability to purify and deliver drugs (e.g., high alcohol content beverages, cigarettes, syringes for drug injections, and more recently vaping devices) along with advances in chemistry that ushered new psychoactive compounds of unprecedented potency (e.g., synthetic opioids, cannabinoids, and stimulants). Access to these highly reinforcing drugs, when combined with promotive environments (e.g., the ubiquity of legal and illegal drugs, chronic stress, peer pressure) and individual vulnerabilities (e.g., preexisting mental illness, chronic pain, genetic predisposition, gender, young age), influence drug experimentation as well as the risk and prevalence of substance use disorders (SUD). The latest example of the potential consequences of such drug-promotive environments is the rising tide of opioid fatalities, initially fueled by misuse of prescription opioid analgesics, then by heroin, and now exacerbated by the misuse of very potent synthetic opioids such as fentanyl. The current opioid epidemic [estimated to have led to over 71,000 opioid overdose fatalities in 2017 (57) and with no signs of abating in 2018 (2)], combined with the high background mortality rate from alcohol (~88,000 annual deaths) (56, 310) and tobacco (>480,000 annual deaths) (58) use, highlights the devastating impact of drugs and addiction in our society.

The application of neuroscientific technologies in humans and laboratory animals has led to remarkable advances in our understanding of the neurobiological underpinnings of drug reinforcement and addiction. As a result, addiction, which has been viewed historically as a "moral deficiency," is being increasingly regarded as a chronic relapsing disorder characterized by an urge to consume drugs and by the progressive loss of control over, and escalation in, drug intake despite repeated (unsuccessful) attempts to resist doing it (334). It is also recognized that addiction emerges in the context of complex biopsychosocial interactions between the pharmacological effects of a drug, individual vulnerabilities (e.g., genetics/epigenetics, developmental stage, existing pathology), inadequate social connectivity, and other sociocultural factors (e.g., normative behaviors regarding drug use, affordability and availability of drugs, legal status). Research on the mechanisms underlying the modulatory influence of adverse social environments, childhood experiences, and genetic variability is fundamental for helping us understand why not everyone who is exposed regularly to a drug becomes addicted (54, 231), and why some addicted individuals can recover while others do not (47, 210, 287).

BOX 1. The endogenous opioid system

The endogenous opioid system modulates the mesolimbic DA system (107, 328) and is implicated in assigning hedonic values to rewards and in integrating reward-related information to guide decision-making and execution of goal-directed behaviors (193). It consists of endogenous opioid peptides and their cognate receptors, namely, β-endorphins, enkephalins, and dynorphins, which signal preferentially through mu (MOR), delta (DOR), and kappa (KOR) opioid receptors, respectively. MOR are responsible for the rewarding effects of opioids and for analgesia, DOR are implicated in analgesia and anxiolysis, while KOR are implicated in the dysphorigenic responses associated with addiction (194) and in stress-induced relapse (136). MOR in the VTA and NAc, as well as in the basolateral amygdala, are implicated in opioids' rewarding effects **(FIGURES 1 AND 2)**. The opioid system also modulates mood, with stimulation of MOR and KOR having predominantly antidepressant and dysphorigenic effects, respectively (250).

BOX 2. The endogenous cannabinoid system

The endogenous cannabinoid system (ECS) modulates other neurotransmitter systems including GABA, glutamate, and DA in key areas along the mesolimbic circuitry (209, 348). The ECS consists of endogenous cannabinoids [anandamide (AEA) and 2-arachidonoylglycerol (2-AG)] and their cognate receptors (CB1R and CB2R) (337). Recent studies corroborate the functional importance of the ECS in modulating reward circuitry (252). For example, activation of CB1R in cortical glutamatergic afferents inhibited DA release in the NAc and blunted reward-driven behaviors (225). In the VTA, 2-AG, and to a lesser extent AEA, released from DA neurons, retrogradely activate CB1R at VTA GABA inputs from GABAergic interneurons **(FIGURE 2)**, or from pallidum or rostromedial tegmental nuclei terminals (252, 271). 2-AG also activates CB1Rs at VTA glutamate inputs arising from cortex (252). Cannabinoids also act in the NAc where medium spiny neurons (MSNs) are modulated by CB1R expressing GABAergic interneurons, and by CB1R expressing glutamate terminals originating from amygdala, hippocampus, and prefrontal cortex (3, 79, 152).

II. DRUG REWARD

Dopamine (DA) lies at the center of drug reward (85, 182). Every drug with addiction potential increases DA, either through direct or indirect effects on DA neurons in the ventral tegmental area (VTA) with the consequent release of DA in the nucleus accumbens (NAc) (357) **(FIGURE 1)**. Drugs of abuse increase DA through their initial action on different molecular targets and, depending on their pharmacological effects **(TABLE 1)**, also engage additional neurotransmitters. Some of these, like the endogenous opioids (**BOX 1**) or the endogenous cannabinoids (**BOX 2**) **(FIGURE 2)**, also contribute to the reinforcing effects of drugs through modulation of hedonic responses or inhibition of negative affective states (232). The significance of non-do-

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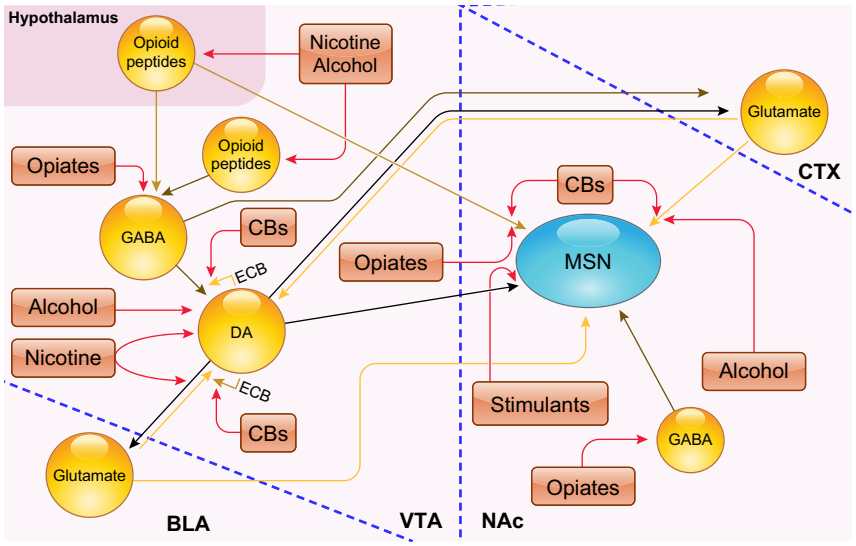

FIGURE 1. Schematic representation of key target sites for various drugs of abuse across the reward circuitry. Ventral tegmental area (VTA) dopamine (DA)ergic neurons project to forebrain targets such as the basolateral amygdala (BLA), medial prefrontal area of the cortex (CTX) or mPFC, and nucleus accumbens (NAc). These neurons receive excitatory synaptic inputs from the mPFC (but also from lateral hypothalamus and pedunculopontine tegmental nucleus/dorsolateral tegmental nucleus; not shown). GABAergic neurons in the VTA target neighboring DAergic neurons as well as projecting to the mPFC and NAc (other inhibitory inputs to these DAergic neurons are likely to arise from extended amygdala output structures; not shown). GABAergic medium spiny neurons (MSNs) in the NAc, which project to either the globus pallidus externus/ventral pallidum (VP) predominantly via D2R-expressing but also D1R-expressing neurons or to the VTA/SN via D1R-expressing neurons, receive dopaminergic input from the VTA. They also receive excitatory inputs from the mPFC and the basolateral amygdala (BLA) (but also from the hippocampus and thalamus). The activity of MSNs is modulated by both cholinergic and fast-spiking GABAergic interneurons (not shown) (312). Drugs of abuse, despite diverse initial actions, produce some common effects on the VTA and NAc. Stimulants directly increase dopaminergic transmission in the NAc. Opiates increase DA indirectly by inhibiting GABAergic interneurons in the VTA, disinhibiting them and by stimulating mu opioid receptors (MOR) on NAc neurons (244). Nicotine stimulates DA neuron firing by its effects on ionotropic (nicotinic) acetylcholine receptors (314). Alcohol, among other effects, increases the firing of VTA DA neurons projecting to NAc via their disinhibition through the inhibition of GABA neurons (238). Cannabinoids (CBs) disrupt the normal endocannabinoid (ECB) signaling–from DAergic neurons on nearby glutamatergic (via retrograde suppression of excitation) and GABAergic (via retrograde suppression of inhibition) terminals–that is responsible for fine-tuning the activity of mesolimbic dopamine projections (31). [Modified from Nestler (244), with permission from Springer Nature.]

paminergic influences on reward processing has not been as extensively investigated as DA's but should not be underestimated. In fact, dopamine-deficient (DD) mice showed conditioned place preference for cocaine [also shown for morphine in naive rats (157)], which appeared to be mediated by serotonin through a mechanism that involves DA neurons, presumably through their release of glutamate or neuropeptides like cholecystokinin and neurotensin (156). Also, studies in genetically engineered mice have shown that the mu opioid receptor (MOR) is not only the main target for heroin and other opioid drugs, but is also essential for the rewarding properties of nonopioid drugs, like alcohol, cocaine, and nicotine (62, 153).

In turn, repeated dopaminergic stimulation from drug use induces neuroadaptations in multiple neurotransmitter systems, including the glutamatergic system, which enhances neuronal excitability and modulates neuroplasticity (286); the GABAergic system, which inhibits action potential transmission (168); and the opioid, endocannabinoid (232, 337, 351), cholinergic (78, 204), serotonin (36, 215), and noradrenergic (109) systems, which modulate affective, hedonic, and aversive circuits in the brain.

Midbrain DA neurons and their projections into the NAc and the dorsal striatum and their GABAergic outputs are implicated in motivating and sustaining reinforced behaviors (including towards food and drugs) but also in avoiding aversive stimuli or states (262). DA neurons in the VTA project to the NAc, which is a central hub of the reward circuit and a major driver of goal-directed actions that are sensitive to the current salience (estimated value) of an associated goal (281). Meanwhile, DA neurons in the substantia nigra (SN) project to the dorsal striatum and translate recurrent reward signals into habitual actions that become increasingly insensitive to actual or updated goal values and are selected instead based on prior experience with the reinforcement associated with that action. The repeated reward-associated behavior, over time, can eventually result in the emergence of habits (103), as the dorsal striatum gradually takes over from the ventral striatum. Additionally, following repeated drug exposures, habits

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Table 1. *Pharmacological targets of main classes of drugs of abuse*

Drug Class	NT Mediators	Mechanism
Opioids	MOR → GABA ↓ → DA ↑	Opioids, like morphine, heroin, or fentanyl, are agonists at MOR (214). Opioid stimulation of MOR in the VTA increases striatal DA release.
Alcohol	EtOH → MOR ↑, NMDA ↓, DA ↑, GABA ↑, ECS ↑	Unlike most addictive drugs that target specific receptors and transporters, EtOH affects a wide range of targets and indirectly increases DA in NAc (354).
Nicotine	nAChRs → DA ↑	Nicotine's interaction with specific nAChRs (i.e., $\alpha4\beta2$) leads to NAc DA release directly by increasing neuronal activity in VTA DA neurons (13, 24) or indirectly by activating modulatory (i.e., GABA or Glu) neurons in VTA (76, 114).
Stimulants	DAT/VMAT2 → DA ↑	Amphetamines block DAT and the VMAT2 (11, 96, 111), which increase synaptic levels of extracellular DA by DAT reversal and depletion of vesicular DA stores, which promotes DA release. Cocaine and methylphenidate block DAT inhibiting DA reuptake, thus increasing DA in NAc (171).
Cannabis	THC → Glu/GABA → DA ↑ ↓	THC activation of CB1 receptors regulates the presynaptic release of both GABA and glutamate, influencing the activity states of the mesolimbic DA system (92, 299) (see **FIGURE 1**)
Classic hallucinogens	5-HT_{2A}Rs > DA ↑; 5-HT_{2C}Rs > DA ↓	Indolamines (e.g., psilocybin, LSD, Mescaline) that display high-affinity agonist activity at serotonin 5-HT_2 G protein-coupled receptor subtypes (5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}) (51). These drugs do not trigger compulsive drug taking and are therefore not considered addictive. Instead, these drugs are predominantly used to alter mental state.
Inhalants	Multiple agents and targets, including volatile substances like toluene, which modulates NMDA ↓, 5-HT_3 ↑, Gly ↑, $GABA_A$ ↑, nACh ↓, and DA ↑ (39, 119, 249)	Abused inhalants (other than nitrites) have a wide range of effects on neurotransmitter release and receptors, with a few similar actions as those of benzodiazepines, alcohol, and barbiturates (15) and have been shown to enhance striatal DA release and have direct reinforcing effects (166).
Benzodiazepines and barbiturates	GABA ↑ > DA ↑	Benzodiazepines and barbiturates enhance GABA by increasing the frequency or the duration of the chloride ion channel opening at the $GABA_A$ receptor, respectively. Both drugs can increase the firing rate of DA neurons in VTA through disinhibition (86, 318).

MOR, mu opioid receptors; VTA, ventral tegmental area; DA, dopamine; NMDA, *N*-methyl-D-aspartate; ECS, endogenous cannabinoid system; NAc, nucleus accumbens; nAChRs, nicotinic acetylcholine receptors; DAT, dopamine transporter; VMAT2, vesicular monoamine transporter 2; THC, tetrahydrocannabinol.

might also result from a reduction in inputs from prefrontal cortex (PFC) into striatum that disrupt the control over action selection (269). However, the notion that "habit" formation is necessary for the establishment of addiction was recently questioned by a study that showed that rodents who had to solve an original problem before gaining access to cocaine did not transfer behavioral control from ventral to dorsal striatum even though they expressed addiction-like behaviors (300). The results from this study are consistent with observations that addicted individuals can display very creative solutions to procure the drug, while falling into ritualistic behaviors once they are consuming them. This indicates that behaviors in addiction are likely a complex combination of adaptive (mostly to procure the drug) and automatic stimulus responding.

VTA DA neurons also project to amygdala and hippocampus, which mediate emotional and memory associations, and to PFC regions, which mediate salience attribution and self-regulation, all of which participate in the reinforcing and conditioning that follow chronic drug consumption. DA neurons in VTA and SN are influenced by projections from multiple brain areas that control their tonic and phasic firing (112). Recent evidence points to significant diversity within the population of VTA DA neurons with respect to their afferent and efferent connectivity (235), their co-release of GABA or glutamate (or both), and the presynaptic receptors expressed in their terminals, which differentially modulate DA release in the presence of other neurotransmitters like GABA or acetylcholine (228). Diversity is also apparent in the cytoarchitectonic, neurochemical, and electrophysiological features of VTA DA neurons as well as in their sensitivity to rewarding versus aversive stimuli (159). Generally, tonic firing of DA neurons (1–8 Hz) sets the background dopaminergic tone, which is sufficient to stimulate the high-affinity DA D2 receptors (D2R), whereas phasic firing (<500 ms; >15 Hz) encodes responses to salient stimuli (rewarding, unexpected, novel, aversive) and results in higher DA levels (120) that are able to stimulate the low-affinity DA D1 receptors (D1R). Thus a drug like cocaine that blocks DA transport back into the terminal, promoting its accumulation in the extracellular space, while also increasing the frequency of DA

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release events in the NAc (9), triggers high DA levels that can activate both D1R and D2R.

The traditional model of the direct and indirect pathways in the dorsal striatum, with their opposing effects on facilitating or inhibiting movement, respectively, has been applied to reward processing by the NAc. Based on this model, NAc D1R-expressing medium spiny neurons (D1R-MSNs) in the direct pathway (midbrain projecting) are proposed to underlie reward and goal directed behaviors, whereas D2R-expressing MSNs (D2R-MSNs) in the indirect (ventral pallidum projecting) are proposed to be associated with avoidance behavior (155). However, recent studies question such a clear segregation of function and anatomic projections for both the dorsal and ventral striatum (187). For example, studies have shown that in the dorsal striatum both D1R-MSNs (direct) and D2R-MSNs (indirect) are activated when initiating an action (75). Moreover, in the NAc, these pathways are less segregated than in the dorsal striatum and D1R-MSNs project directly both to the midbrain and to the ventral pallidum, which is modulated both by D1R-MSNs and D2R-MSNs (277), and the D2R-MSNs that project to ventral pallidum directly disinhibit the thalamus (186). In the NAc, studies in rodents reported the existence of a subpopulation of neurons that coexpress D1R and D2R (145) and form a D1R-D2R complex that when activated inhibits basal natural and cocaine reward (146).

In the VTA, spontaneous firing of DA neurons sets tonic DA levels, which stimulate mainly D2R (also D3R, which have high affinity for DA) in NAc, upon which phasic DA firing can be superimposed resulting in higher DA levels that additionally stimulate D1R (262). Although an unexpected reward triggers phasic DA firing, its repeated presentation transforms it into an expected reward and causes the phasic firing of the DA neuron to occur upon exposure to the predictive cue (making it conditioned). In contrast, there is a pause in DA neuron firing when an expected reward does not materialize (making it discordant). In this way, when an outcome differs from what is expected, DA signals a "reward prediction error" regardless of its positive or negative valence, that recent studies suggest may reflect not just its scalar reward value but additional dimensions of the expected outcome, such as its characteristics or presentation sequence (189). Drug cues trigger phasic DA firing, which in the NAc binds to both D1R-expressing MSNs, where DA is stimulatory (increases cAMP and intracellular Ca signaling), and D2R-expressing MSNs where DA is inhibitory (decreases cAMP and intracellular Ca signaling) (213, 245, 297, 298), sparking the motivation to initiate reward-directed behaviors (346). Although it was believed that aversive stimuli or their cues, by reducing tonic activity of DA neurons and DA release in NAc, lowered D2R-inhibition of indirect pathway MSNs, leading to avoidance behavior, this, as discussed above, is now being questioned. Indeed, some DA neurons are activated, not inhibited by aversive stimuli (352), but further research is needed to characterize their projections into NAc and other brain regions (186). Additionally, both tonic and phasic firing stimulate the high-affinity D3R, which are highly expressed in NAc, where they colocalize with D1R potentiating their signaling (108) and possibly modulating drug reward and conditioning (117). The NAc also expresses D5R, which colocalize with D1R in MSNs (239), are also expressed in interneurons, and appear to play distinct roles in neuroplasticity relative to D1R (59). The D4R is also expressed in the NAc, and genetic studies have implicated its encoding gene (*DRD4*) in addiction vulnerability (255), whereas preclinical studies have shown that it modulates the pharmacological effects of drugs. However, it is clear that the functional differences between DA receptors, their colocalization, and interactions in NAc (including that between D3R and D5R, which has been minimally investigated) require further investigation.

Phasic DA firing and stimulation of D1R are needed for drug reward and for eliciting conditioned associations. On the other hand, DA stimulation of D2R signaling is associated with motivational drive (306) but, depending on the circumstances, can interfere with the reinforcing effects of drugs such as with exposure to multiple alternative reinforcers. Notably, positive reinforcement and maximal reward occur when both D1R and D2R are simultaneously stimulated in the NAc, but additional studies are needed to disentangle how each receptor subtype contributes to the overall effect (311).

III. DOPAMINE AND NEUROPLASTICITY

Drugs, via excessive and repeated dopaminergic stimulation, induce persistent neuroplastic adaptations in midbrain DA neurons and in their projections into NAc and also into dorsal striatum that are believed to underlie conditioning along with the enhanced incentive saliency to drug cues and behavioral inflexibility (128, 262, 293). When conditioning is established, DA neurons fire when exposed to the drug-predictive cues that precede the drug's arrival, in effect predicting an imminent reward. Conditioning can be instantiated for many types of cues, including places and people associated with the drug experience, or mental states that predominated at the time when the drug was being consumed (depressed, bored, excited, stressed, etc.), all of which can subsequently awaken, by themselves, the motivation to seek the drug (289, 343). These neuroadaptations prominently involve glutamatergic inputs onto DA neurons in VTA and into MSNs in NAc setting up the stage for the respective behavioral changes in reward responsivity and habituation that characterize addiction, including a persistent risk of relapse that makes treatment so challenging (176, 290, 359). Some of the key drug-induced adaptations are similar to synaptic changes associated with learning including changes in dendritic morphology, ionotropic glutamate receptors (predominantly AMPA and NMDA receptors) that result in long-term potentiation (LTP) and long-term depression (LTD) (138, 176). Synaptic strength is modulated presynaptically through the regulation of glutamate release

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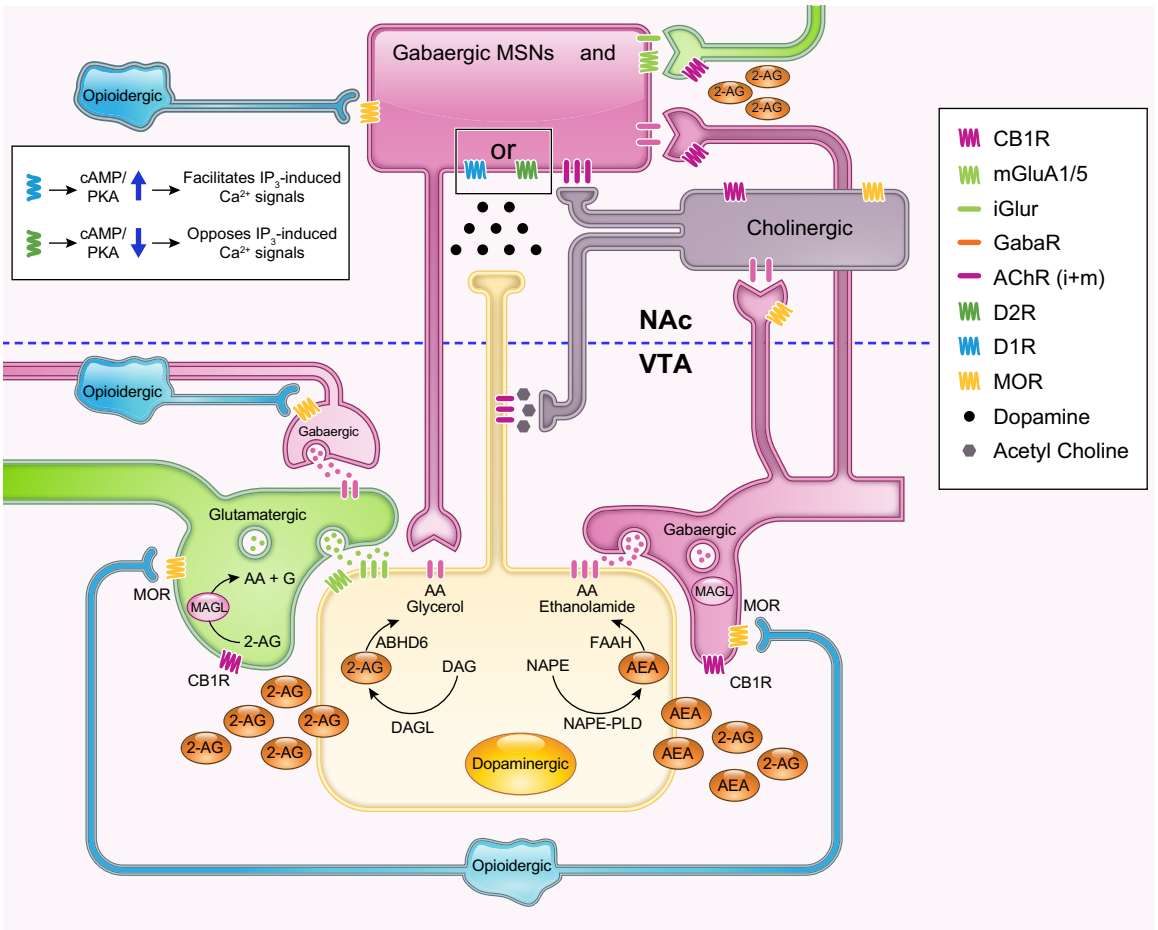
and postsynaptically by the insertion or removal of transmembrane glutamate ionotropic receptors (NMDA and AMPA) and by changes in their subunit composition, which modifies their efficacy. Glutamate release in NAc is decreased by activation of metabotropic glutamate receptors mGluA2/3 (362), adenosine A1 receptors (37), D2R (154), or cannabinoid CB1R (272, 316). Postsynaptically, trafficking of AMPA and NMDA receptors is regulated by D1R activation, which promote AMPA surface expression. The insertion of high calcium-permeable AMPA receptors that lack the GluA2 subunit is necessary for the expression of incubation of cocaine craving (106). Increases in NMDA receptors containing the GluN2B subunit have also been associated with neuroplasticity after chronic cocaine or heroin (160, 294, 349). Postsynaptic mGluR1 produce an LTD that reverses cocaine-induced increases of high calcium-permeable AMPA receptors in VTA (220) and in NAc where it reduced cue-induced cocaine craving (211).

Morphological changes occur in parallel to the strengthening of excitatory synapses, which is associated with larger synapses, whereas weakening results in smaller synapses and reduced dendritic spine density. In addition, recent studies in transgenic mice indicate that chronic administration of cocaine is also associated with specific structural plasticity in dopaminergic boutons in the NAc shell (91) **(FIGURE 3)**.

However, our understanding of drug-induced neuroplasticity is evolving. For example, with the use of a modified reinstatement protocol, it was shown that cocaine-induced neuroplastic changes in dendritic spine morphology and AMPA/NMDA ratios were temporarily reversed by cocaine use (308). Also, while most glutamatergic synapses contain both AMPA and NMDA receptors, a small number of so-called silent (also referred to as "AMPA silent" or immature) synapses express NMDA receptors exclusively (203), and have been associated with chronic stress (315) and with addictive and neurodegenerative disorders (144). For example, silent synapses are produced in response to cocaine (in NAc) (89) and alcohol (in dentate gyrus) (23). However, these synapses do not contribute significantly to stimulus (i.e., drug) evoked excitatory postsynaptic currents. Thus it has been hypothesized that, by recapitulating some key aspects of the immature yet more "teachable" developing brain (89), silent synapses might provide a "metaplasticity" signal and prime the circuitry for any needed subsequent plastic changes (e.g., LTP or LTD) (217).



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Furthermore, the identification of Maged1, implicated in the modulation of dendritic spine density and learning in the hippocampus (363), as a gene whose expression in PFC is essential for both extracellular DA release in NAc and behavioral sensitization to cocaine (82), illustrates another molecular process involved both in learning and in drug-induced neuroplasticity in PFC and NAc. Similarly, synapses from hippocampal glutamatergic terminals into the NAc were shown to also undergo LTP, which was necessary for the formation of reward-related contextual memories, although these neuroplastic changes did not appear to be DA-dependent (196).

There is also increasing evidence that in addition to Hebbian neuroplasticity, some forms of drug-induced neuroplasticity in NAc are homeostatic and interact with Hebbian neuroplastic changes (90, 161, 172, 290). For example, increases in synaptic strength following repeated cocaine exposure trigger homeostatic changes in membrane excitability in MSNs in the NAc, which appear to contribute to incubation of cocaine craving (349).

IV. NEUROCIRCUITRY OF ADDICTION

The percentage of laboratory animals that show addictive-like behaviors, or of people that become addicted to a drug after repeated exposure, varies as a function of the drug, being higher for drugs like heroin or methamphetamine and lower for drugs like alcohol or cannabis. For example, only between 15 and 20% of rats chronically exposed to cocaine will continue to compulsively prefer cocaine over other rewarding options (52), whereas the percentage of heroin-preferring rats can go as high as 50% under similar experimental conditions (198). These percentages, however, do vary across different rat strains, highlighting the role of genetics in modulating drugs' effects. Epidemiological data are generally consistent with this picture. According to the best available estimates, the odds, in lifetime drug users, of ever becoming addicted to alcohol, cannabis, cocaine, or opioids (heroin) are ~1.5, 9, 17, and 23%, respectively (7). As of now, it is not clear what determines the transition from drug experimentation to addiction, which emerges when individuals lose their ability to overcome the strong urge to take the drug despite a conscious awareness of not wanting to do so and the recognition of their potentially catastrophic consequences. However, we do know this transition is associated with measurable disruptions in several brain circuits including those involved with conditioning, reward sensitivity, incentive motivation, self-monitoring/regulation, mood, and interoception. In this review, we use the term *addiction* in correspondence with the dimensional definition of moderate to severe SUD as per the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) **(TABLE 2)**.

A. Conditioning

A key process that initiates the transition into addiction and helps perpetuate it is the consolidation of conditioning to

FIGURE 2. Schematic simplified cartoon showing some of the indirect modulatory effects of midbrain (ventral tegmental area, VTA) opioid and endocannabinoid signals on dopaminergic transmission in nucleus accumbens (NAc). Reward-related stimuli conveyed through glutamatergic afferents (green) promote burst firing of dopamine (DA) neurons (yellow) mainly driven by ionotropic glutamate receptor (iGluR) binding activation at the dopaminergic cell. The level of activation is normally kept in check by GABAergic counterbalancing inputs (pink), but also by direct inhibitory GABAergic input inhibiting presynaptic glutamate release (66). Endogenous [released from opioidergic neurons (light blue), mostly projecting from the hypothalamus] or exogenous (natural or synthetic opioid like molecules) opioids activate endogenous mu opioid receptors (MOR) on GABAergic interneurons. The MOR is coupled to inhibitory G proteins, whose activation (by an endogenous peptide like endorphin or exogenous agonists like morphine and fentanyl) leads to a dissociation between the Gα and G$\beta\gamma$ subunits and the activation of intracellular effector pathways. One such pathway leads to the inhibition of GABA release as a result of increased conduction of potassium ions, which hyperpolarizes the cell making it less responsive to depolarizing inputs and inhibiting calcium influx (123). In addition, activation of MOR increases mitogen-activated protein kinase (MAPK) signaling while their phosphorylation activates the arrestin pathway (5), which has the ability to desensitize, activate, and control the trafficking of G protein-coupled receptors (GPCR) (140). A drop in GABAergic tone causes a net disinhibition of the neighboring dopaminergic neuron and the release of excess dopamine (black dots) onto direct and indirect medium spiny neurons [pink medium spiny neuron (MSN)], which reinforces the euphorigenic effects of opioids. Ionotropic GluR-mediated activation of the DA neuron leads to Ca^{2+} influx (via voltage-gated calcium channels), which is either facilitated or hampered in D1R vs D2R expressing MSN populations, respectively (317) (*inset*), leading to their differential roles in plasticity. At the same time, the Ca^{2+} influx, combined with activation of mGluA1/5, triggers the "on demand" production of 2-arachidonoylglycerol (2-AG) from diacylglycerol (DAG) [or anandamide (AEA) from *N*-acyl-phosphatidylethanolamines (NAPE)]. Retrograde 2-AG transmission through CB1 receptor binding on monoacylglycerol lipase (MAGL) containing afferent (GABA and Glu) neurons has the net effect of disinhibiting dopamine neurons and facilitating phasic DA release (63). This is because cannabinoids (e.g., tetrahydrocannabinol, 2-AG) operate as full agonists at GABA terminals [that display a high CB1R to vesicles ratio (188)] but as partial agonists at Glu terminals [where the CB1R-to-vesicles ratio is much lower (295, 296)]. As shown, AEA is assumed to be retrograde in spite of data showing that FAAH is predominately postsynaptic while NAPE PLD is presynaptic. The true nature of AEA neurotransmission remains unclear partly because there are other pathways for AEA synthesis. In the NAc, GABAergic projections, sent by the VTA, also synapse onto cholinergic interneurons (dark gray), thus inhibiting their excitatory input onto DA terminals. Activation of either CB1 or MOR on these GABA neurons can stimulate DA terminals (independently of VTA DA neuron activation) by disinhibiting ACh release while activation of these receptors, which are also expressed on ACh interneurons, could in theory have the opposite effect on DA levels in the accumbens (351). GABAergic and glutamatergic terminals in the NAc also have the capacity to modulate accumbal DA activity onto MSNs directly. Since these neurons also express MOR [but some also CB1R (226, 361)], their activation on GABA inputs could enhance DA release, while their inhibitory effects on glutamatergic inputs could reduce accumbal release of DA.

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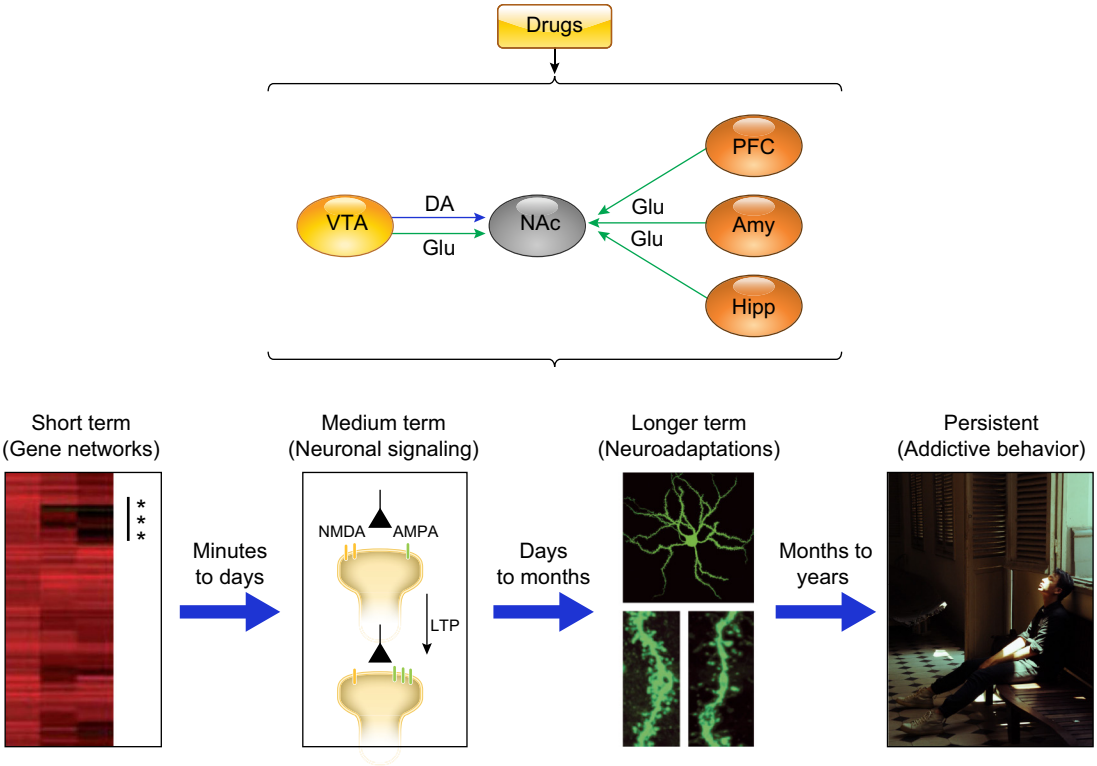

FIGURE 3. Leading hypothesis of how a temporally coordinated cascade of drug-induced changes in synaptic activity hijack multipurpose learning processes to engender maladaptive and persistent addictive behaviors. VTA, ventral tegmental area; DA, dopamine; PFC, prefrontal cortex; Amy, amygdala; Hipp, hippocampus. Bottom figures depict (from *left* to *right*) a heat map of genes upregulated (*) in the nucleus accumbens (NAc) 1 h after acute cocaine administration to naive animals (275); examples of such transient transcription and epigenetic modulatory events include regulatory and signaling genes like fosB, ΔFosB, NFκB, CdK5, and MEF2. [From Robison and Nestler (275), with permission from Springer Nature.] Drug-induced changes in neuronal activity (e.g., changes in NMDA/AMPA receptor balance) lead to synaptic plasticity (e.g., LTP) in the reward circuitry (169). [From Jones and Bonci (169), with permission from Elsevier.] Morphological and functional changes, like increased dendritic spine density, which, if sustained, can lead to cytoskeletal and circuit remodeling, a phenomenon that correlates with synaptic strength and the strength of drug-associated memories in vivo, which, over a period of months and years, contributes to the orchestration and cementing of stereotypical addictive behaviors. [From Nestler. *Dialogues Clin Neurosci* 15: 431–443, 2013.]

the drug. As addiction develops there is an expansion in the number of stimuli that become experientially linked (conditioned) to the drug, and thus a greater likelihood of being exposed to a drug-predictive cue. Any encounter with these cues can trigger bursts of DA in the NAc (259) and lead to further consolidation in dorsal striatum; this directs the attention to the drug-predictive cue and engenders the motivation to procure the drug. As a result, the motivational drive toward the drug now occurs before the drug is consumed and is triggered by the exposure to the drug-predictive cue. Upon drug consumption, the continued DA stimulation from the drug's pharmacological effects promotes continued ingestion while further strengthening conditioned learning, thus perpetuating the cycle of relapse and drug-taking.

One of the changes believed to contribute to enhanced reactivity to drug-predictive cues in addiction is the disruption of the balance between D1R and D2R signaling in the ventral striatum. Overall, rodent studies provide support to the notion that strengthening of D1R-MSNs in NAc enhances cocaine reward, whereas strengthening of D2R-MSNs suppresses it (49, 208, 323). Similarly, a recent study reported that cue-induced reinstatement was intensified by either activating D1R-MSNs or reducing the activity of D2R-MSNs (151). Combined, the studies suggest that the motivation to take the drug in addiction is energized by drug-predictive cues and by drug-induced transient DA-induced stimulation of D1R (activating D1R-MSNs) concomitant to a weakening of signaling from D2R that is insufficient to counterbalance D1R-MSNs, thus facilitating compulsive intake. Using optical imaging in transgenic mice, we showed that in the dorsal striatum of naive mice, acute cocaine led to fast [Ca^{2+}] increase in D1R-MSNs and to progressive [Ca^{2+}] decreases in D2R-MSNs, consistent with DA stimulating D1R-MSNs and inhibiting D2R-MSNs (213). In contrast, in mice chronically exposed to cocaine, the [Ca^{2+}] responses to acute cocaine were blunted but to a significantly greater extent in D2R-MSNs than in D1R-MSNs, unbalancing the relative signaling towards a

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Table 2. *Diagnostic criteria for substance use disorder based on DSM-5*

DSM 5 SUD Criteria
1. Hazardous use
2. Social/interpersonal problem related to use
3. Neglected major roles because of use
4. Withdrawal
5. Tolerance
6. Used larger amounts/longer
7. Repeated attempts to quit/control use
8. Much time spent using
9. Physical/psychological problems related to use
10. Activities given up in order to use
11. Craving

A mild substance use disorder (SUD) is diagnosed with 2–3 criteria, moderate with 4–5, and severe 6–7 criteria (147). DSM-5, *Diagnostic and Statistical Manual of Mental Disorders*.

predominance of D1R-MSNs over D2R-MSNs (251). However, studies are needed to assess if similar changes occur in NAc and their association with compulsive drug taking, particularly since there is evidence that in the NAc there is coexpression of D1R and D2R and of projections of both D1R-MSNs and D2R-MSNs into ventral pallidum.

Unbalancing D1R over D2R signaling with repeated drug exposure would favor cue-induced phasic DA firing and D1R signaling (driving drug-seeking) while undermining tonic DA firing and D2R signaling (which opposes prepotent responses). Specifically, upregulation of the low-affinity D1R would favor signaling from phasic DA responses, while decreasing the sensitivity to tonic DA responses due to a downregulation of the high-affinity D2R. In contrast, an upregulation of D2R would enhance the sensitivity to tonic DA release while attenuating phasic DA release via D2R autoreceptor inhibition and might explain why D2R upregulation inhibits compulsive cocaine taking (323). Unbalancing D1R over D2R would enhance the reinforcing values of drugs and drug-predictive cues while undermining the capacity for behavioral control, facilitating impulsive and compulsive drug consumption (213). In clinical studies, the enhanced sensitivity to conditioned drug-predictive cues has been associated with addiction severity (343) and with worse clinical outcomes (68, 185). Thus a better understanding of the relationship between D1R and D2R dynamics in NAc and dorsal striatum has significant translational implications for addiction treatment. For example, a rodent study that showed that optogenetic activation of glutamatergic inputs onto accumbal D2R-MSNs reduced cocaine self-administration suggests that strengthening signaling through D2R-MSNs could be beneficial for the treatment of addiction (34).

B. Reward and Motivation

In parallel to the enhanced sensitivity to the expectation of the drug's rewarding effects (due to conditioning), there is a reduced sensitivity of the DA reward circuit to the actual consumption of the reward, which has been observed in drug addicted individuals and interestingly also among some obese individuals who display some phenotypic traits consistent with "food addiction" (326). This reduced sensitivity in drug-addicted individuals extends to non-drug rewards with the concomitant decrease in their motivational value, which contributes to the lack of interest in non-drug-associated activities characteristic of addiction. Brain imaging studies of drug-addicted individuals have helped characterize these adaptations by revealing decreased D2R expression and DA release in the striatum (both dorsal and ventral regions) (339; though see negative studies in Refs. 95, 175). Very few studies have evaluated D1R in addiction or in animal models of addiction, and the results are inconsistent. For example, chronic cocaine in non-human primates has been reported to decrease D1R in a specific subregion of the ventral striatum that encompasses the NAc (234), although they appear to recover after 90 days of abstinence (25), whereas neither electrophysiological studies in cocaine-exposed rats (227) nor brain imaging of cocaine users have found changes in D1R (224), even though the levels were predictive of cocaine intake in cocaine users (224). On the other hand, postmortem studies in methamphetamine users reported significant increases in D1R in NAc (360), whereas brain imaging studies showed no differences in D1R availability (247). These inconsistencies likely reflect in part the paucity of data, differences between methodologies (in vitro vs. in vivo measures), and differences in species and animal models used. Moreover, DA is a neuromodulator, so its effects are state-dependent, which may account in part for why DA stimulation can result in opposite effects depending on the context in which it occurs (291).

Imaging studies have also revealed decreased activation of brain reward regions to receipt of non-drug rewards, such as food, sexual stimuli, or money, in individuals addicted to drugs compared with controls (6, 33, 53, 99, 253). Such a reduced sensitivity to non-drug rewards is likely to impair an addicted individual's capacity to be incentivized by naturally pleasurable activities and stimuli. Intriguingly, there is also a reduced reactivity of striatal and prefrontal regions to negative reinforcers, which is associated with worse outcomes (30). Decreased sensitivity to negative reinforcers could impair the capacity of the addicted person to feel deterred by negative outcomes (e.g., incarceration, loss of child custody).

C. Self-Regulation

The development of the powerful cue-conditioned cravings outlined above becomes even more deleterious when com-

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bined with growing deficits in the brain's ability to inhibit maladaptive behaviors and prepotent responses. This is because deficits in self-control can contribute greatly to an individual's inability to avoid risky or self-destructive behaviors, resist temptation (such as taking drugs), or delay gratifications (such as future payoff of engaging in a long-term recovery program), and thus increasing his/her vulnerability to addiction (335).

There is both preclinical and clinical evidence consistent with the notion that the weakening of self-control mechanisms correlates with impaired performance in PFC circuits secondary to drug-induced adaptations in striatal networks or sometimes by direct harm to PFC (320, 356). Brain imaging studies in humans have shown that, in the striatum, D2Rs are positively associated with baseline metabolic activity (marker of brain function) in frontal cortical regions and inversely associated with the sensitivity to the rewarding effects of psychostimulant drugs (102, 341, 342), whereas preclinical studies in rodents have shown that D2R upregulation interferes with drug consumption (323, 324). Clinical imaging studies also show that the reduced striatal D2R seen in human addiction is associated with decreased baseline metabolic activity in prefrontal regions including the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), and dorsolateral prefrontal cortex (DLPFC) (reviewed in Ref. 345; see also Refs. 333, 336, 340, 344). Since OFC, ACC, and DLPFC are implicated in salience attribution, inhibitory control/emotion regulation, and decision-making, respectively, it is reasonable to hypothesize that faulty modulation of these regions by striatal D2R is likely to underlie the enhanced motivational value of drugs, the significant loss of control over drug intake among addicted individuals (335), and the compulsive and impulsive drug intake seen in addiction (129). Moreover, subjects at high risk for alcoholism (positive family history) but who did not suffer from alcoholism showed upregulation of striatal D2R that was associated with normal baseline activity of the OFC, ACC, and DLPFC. This finding stands in sharp contrast to the hypoactivity seen in these same frontal regions of individuals affected by alcoholism and other addictions, prompting the hypothesis that striatal D2R upregulation could have protected unaffected individuals against alcoholism by regulating circuits involved in self-regulation (340). Indeed, prospective imaging studies of brain development are increasingly revealing that abnormalities in PFC constitute a vulnerability risk for SUD (see sect. V) (170).

Animal studies also corroborate the presence of neuroadaptations in mesocortical DA synapses in the PFC as well as in corticofugal glutamate synapses in the NAc in rodents withdrawn from chronic cocaine exposure (173). The former appears to involve a partial decoupling between $G_i\alpha$ and D2R (40), and may contribute to an exaggerated reactivity towards drugs and drug-predictive cues and to a blunted response towards natural rewards. The latter relies on cellular adaptations leading to reduced levels of extracellular glutamate in NAc (12) that might also contribute to compulsive drug seeking.

The stimulation of D2R, through tonic DA firing (implicated in motivation), without concomitant phasic firing (implicated in associative learning) (142), can oppose drug consumption through its modulation of PFC regions involved with self-regulation (149). It is recognized that dopaminergic signaling via D2R in the PFC modulates its function, including inhibitory control and cognitive flexibility, where D2R signaling appears to be dependent not only on G_i but also G_s (enhancing the excitability of cortical pyramidal neurons) (274). Indeed, optogenetic stimulation of the prelimbic cortex in cocaine-exposed rats prevented compulsive cocaine seeking, whereas its inhibition enhanced it (64). Similarly, induction of tonic activity in VTA DA neurons, which project to infralimbic and prelimbic PFC, reduced ethanol self-administration (17). Moreover, the function of the PFC in addicted individuals has been shown to predict clinical outcomes, a disrupted connectivity between PFC and striatal regions being a consistent finding among individuals addicted to various drug classes (326). The importance of PFC regulation of striatal activity in addiction phenotype in rodents was recently shown in an optogenetic study that showed that increased connectivity between the OFC [presumably infralimbic PFC (192)] and the dorsal striatum predicted compulsive self-stimulation of VTA DA neurons despite receiving noxious electric shocks (254). In this study, optogenetic inhibition of the OFC projecting terminals into the dorsal striatum inhibited compulsive self-administration. The distinct projections from the various PFC regions to the dorsal and ventral striatum are likely to account for why, in contrast to these findings, the optogenetic stimulation of the prelimbic PFC decreased compulsive cocaine consumption, whereas its inhibition increased it (64). As such, the PFC has been a target of transcranial magnetic stimulation (TMS) (**BOX 3**) and transcranial direct electrical stimulation (tDCS) (**BOX 4**) interventions for the treatment of SUD, most of which have targeted the DLPFC. The PFC is also the target for behavioral interventions aimed at strengthening executive function and decreasing the incentive salience of drugs and drug cues, in part via exposure to alternative reinforcers as a means to facilitate and support recovery.

D. Negative Mood and Stress Reactivity

An important component of the addicted state is the behavioral shift that is typically observed from seeking the reward for its positive reinforcing value towards seeking it to avoid negative reinforcement (338). This state, which has been described as the "dark side" of addiction, is most evident during acute drug withdrawal and is associated with a high risk of relapse as a means to temporarily escape the experience of intense distress and negative emotionality (184).

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BOX 3. TMS as a potential addiction treatment

TMS is a noninvasive technique with the potential to reduce the long-term neurophysiological (and behavioral) changes induced by chronic drug use. Although it is premature to judge its effectiveness, initial results are encouraging. For example, in one pilot study (open label), high-frequency (excitatory) TMS delivered to the left DLPFC of patients with cocaine use disorder led to significant reductions in cocaine use and craving (322). Other preliminary results also support the idea that TMS could help patients control their cravings (263, 267) and cocaine consumption (35). The few studies exploring the use of TMS for the treatment of methamphetamine addiction have yielded promising but somewhat less consistent results (201, 206, 313). In addition, a recent smoking cessation trial using TMS targeting the DLPFC and insula, bilaterally, resulted in significantly reduced cigarette consumption and nicotine dependence scores that acted synergistically with concomitant cue exposure therapy (88). Clearly, more research and larger clinical studies will be needed to identify the source of some conflicting results (98), optimize TMS parameters for different indications, and ascertain the full therapeutic potential of TMS in addiction. However, the clear antidepressive properties of high-frequency TMS to the left DLPFC (45, 260), and the promise of low-frequency TMS (to OFC or supplementary motor area) for treating obsessive compulsive disorders (22), highlight its therapeutic potential for addiction, which shares key nosological features with these conditions. For these reasons, TMS has also emerged as a promising technique to treat patients with comorbid SUD and other mental illnesses (73, 325, 331).

BOX 4. tDCS as a potential addiction treatment

tDCS is an alternative noninvasive brain modulation technique with therapeutic potential whereby some (hard to assess) portion of the current penetrates through the scalp affecting cortical excitability. Six of seven tDCS studies found significant reductions in alcohol-related craving or consumption after the treatment, whereas five of eight studies found significant reductions in nicotine cravings and/or consumption (reviewed in Ref. 70). Only two proof of principle studies investigated PFC targeting tDCS for reducing cocaine (18, 80) and while results were positive, the sample sizes were too small (11 and 17 subjects, respectively) and replication is needed. Reductions in craving were also reported in a study of 20 heroin-addicted individuals treated with tDCS targeting the fronto-temporal-parietal area (350). Similarly, bilateral tDCS targeting the DLPFC of methamphetamine users significantly decreased craving while modulating the functional connectivity of brain networks (DMN, executive control, and salience) (292).

Neuroimaging studies suggest the therapeutic effects of tDCS (as well as of TMS) could be mediated through its ability to modulate DA (69) in some of the brain areas where DA dysregulation could lead to impaired executive function and reward (113). However, much more work is required for understanding the mechanisms of action of transcranial stimulation techniques and their potential for treating addiction, including optimization of therapeutic protocols (stimulation frequency, dosing, location) and the possibility of personalized interventions based on the specific brain circuitry dysfunction of the addicted individual.

This distress is associated with reduced DA signaling in response to rewards (anhedonia) but also with an enhanced sensitivity of the brain's stress system, including the extended amygdala, habenula, and hypothalamus (183, 273). Negative emotional states have been characterized in humans during acute and protracted abstinence from all major drugs of abuse (8), a phenomenon consistently replicated in animal studies (reviewed in Ref. 183) that contributes to the relapsing nature of addiction and likely also to its high comorbidity with depression, anxiety, and suicidality (1, 276).

Similar to typical stressors, like childhood neglect (122), acute exposure to drugs activates the hypothalamus-pituitary-adrenal (HPA) axis via the corticotropin releasing factor (CRF) (reviewed in Ref. 273), which stimulates production of ACTH in the anterior pituitary and, secondarily, cortisol by the adrenal cortex. In turn, HPA axis activation influences brain circuits involved in drug reward and the acquisition of drug-seeking behavior. Stress induces reinstatement of drug-seeking behavior in animal models of drug consumption, exemplifying the link between reward and stress systems (221). Molecules implicated in the regulation of stress-induced reinstatement include CRF, norepinephrine, DA, glutamate, dynorphin, hypocretin, neuropeptide Y, and others (221). These messengers act at various sites that include the bed nucleus of the stria terminalis (BNST), central amygdala, VTA, NAc, habenula (38, 266), dorsal raphe, locus coeruleus, and several PFC regions (221). CRF activation can translate an aversive event (e.g., social defeat, foot-shock) into robust DA increases in NAc, which though seemingly paradoxical, reflect the fact that CRF acts on a specific subset of DA VTA neurons (158) that are tuned to aversive rather than rewarding stimuli (159).

E. Interoceptive Awareness

The transition from flexible, goal-directed to reflexive, compulsive behaviors is also influenced by interoceptive and exteroceptive inputs. The insula, particularly its most anterior region, plays a major role in interoception through its involvement in sensing and integrating information about the internal physiological state (in the context of ongoing activity) and conveying it to the ACC, ventral striatum, and ventral medial PFC to initiate adaptive responses (256). The bidirectional communication between the insula and these limbic regions suggests a role in the integration of autonomic and visceral information (including information conveyed from the vagal nerve to the nucleus tractus solitarius) with emotive and motivational information that enables the conscious awareness of internal urges.

The relevance of the insula to addiction first emerged with a seminal study that showed that smokers with insular lesions (due to stroke) were able to quit smoking with remarkable ease, without cravings or relapse (243). Since then, multiple imaging studies have shown differential activation of the anterior insula during craving for nicotine (236), cocaine (278), and alcohol (285) and of the middle insula with cocaine and

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cigarette craving (20, 216). As such, insular reactivity has been proposed to offer a potential biomarker for relapse risk (164) and a target for TMS and tDCS as addiction treatments (94, 218) (BOXES 3 and 4).

The enhanced engagement of interoceptive processes in addiction also recruits the default mode network (DMN), which is also modulated by DA (242, 327). The DMN is involved in self-awareness and mind wandering, and its enhanced activation in the addictive state might redirect exaggerated attention towards the internal state of craving or discomfort. Not unexpectedly, imaging studies have revealed that addiction is associated with impairment within regions that are part of the DMN as well as between the DMN and other functional brain networks (364). This includes studies showing disrupted activity or connectivity of the ACC (part of the anterior DMN) and insula (202, 243). Additionally, neuroimaging studies have also revealed alterations in the precuneus (increased activation to drug-predictive cues and connectivity), a key region within the posterior DMN involved with the internal awareness of the perception of environmental stimuli (exteroception) and for self-monitoring in addicted individuals (84).

V. VULNERABILITY FACTORS

Repeated exposure to a drug of abuse is a prerequisite for the development of drug addiction, but its overt clinical manifestation depends heavily on interacting biological, environmental, and psychosocial factors.

A. Genetics and Epigenetics

Genetic variation plays a significant role in establishing interindividual differences in addiction risk. Studies focused on variability among identical and nonidentical siblings have produced a rough estimate of ~50% for the contribution of genetic differences to overall addiction risk. Genetic studies have reported an overlap in genetic variants that influence risk towards different classes of drugs (332), and the largest study to date on 1.2 million individuals that assessed common genes in alcohol and nicotine use has identified genes involved with dopaminergic and glutamatergic neurotransmission, genes involved with transcription and translation, and with brain development (205). They have also revealed that an important genetic contributor to SUDs appears to operate through a general purpose underlying mechanism (i.e., a shared predisposition) that influences a vulnerability for disorders characterized by pathological tendencies to violate social norms or to engage in oppositional behaviors (clustered as disorders with externalizing tendencies) (178), providing a link to the heterogeneous construct referred to as impulsivity (87). However, common genetic vulnerability has also been reported for SUD and internalizing disorders (282), providing a link for the frequent comorbidity between SUD and anxiety and depression (207, 268). In addition to these common genetic factors, studies have also identified genetic variants that are mostly specific for a given drug. Most notable are the genetic variants that encode for the alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) enzymes that lead to impaired metabolism of alcohol and that provide protection against alcoholism (74).

Multiple genome-wide association studies (GWAS) have identified genetic variants associated with specific drug addictions (28, 143, 279) (see Supplemental Table 1; https://github.com/rubenbaler/PRV-00014-2018R1/blob/master/ST.1.docx). However, like other complex biobehavioral disorders, addiction is a polygenic disease likely hinging on multiple genes and genetic networks (205, 229). Addiction-associated gene variants can impact the risk of abuse and addiction via direct or indirect influences on neurotransmitter systems, drug metabolic pathways, neural circuitry, cellular physiology, brain development, and personalities and traits (e.g., novelty seeking, impulsivity) that influence the behavioral responses to environmental stimuli. Although genetic research of addiction has not yet translated into novel therapeutics for SUD (105, 199, 261), there has been steady progress towards the identification of genetic biomarkers with translational potential for nicotine addiction (21, 29) and opioid use disorders (OUD) (32). Because genetic background can dramatically alter the phenotypic expressivity of different sets of genes, studies are needed to tease out modifier loci in diverse populations and the epigenetic modifications regulating them (104, 261, 264). Moreover, genetic findings offer clues as to which molecular networks might underlie the associations with addiction, thus expanding the array of potential targets for therapeutics development. This, coupled with systems biology analyses that examine Gene × Gene, Gene × Environment, and Gene × Environment × Development interactions are promising future strategies for therapeutics development and for identification of biomarkers.

Genetic studies have helped advance our understanding of the neurobiological processes involved in addiction. For example, the finding that a polymorphism in the $\alpha 5$ nicotinic receptor is associated with an increased risk of nicotine addiction triggered attention to the role of the habenula, which displays a substantial concentration of $\alpha 5$ nicotinic receptors (197) and also of MOR (118). This has revealed that the habenula is not only implicated in nicotine addiction but that it also participates in the negative affective states associated with the chronic use of various drugs of abuse, including alcohol (174) and opioids (222).

Our expanded understanding of how epigenetic modifications regulate the enhancement or silencing of gene expression has also led to studies that are beginning to characterize the effects of drugs on epigenetic marks in various brain

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regions as well as their involvement in the addiction process (261, 347). Arguably, much of the information comes from studies focused on the effects of repeated cocaine exposure on DNA methylation and posttranslational modifications of histone proteins that regulate the accessibility of DNA to the transcription machinery via a dynamic process of chromatin remodeling. For example, systemic administration of sodium butyrate, a general histone deacetylase (HDAC) inhibitor, facilitates extinction of a previously established cocaine-conditioned place preference in a mouse model of addiction (219). This result is consistent with previous studies showing that some of the behavioral effects of chronic cocaine are associated with the recruitment of HDACs to reduce histone acetylation and gene activity (270). Some of the drug effects in the modulation of gene expression are rather generalized, while others are gene and/or paradigm specific. For example, in the striatum, hyperacetylation of H4 at specific chromatin locations along the *cFos* gene promoter (with its concurrent transcriptional activation) occurs after acute but not chronic cocaine administration. In contrast, hyperacetylation of H3 at the *Bdnf* and *Cdk5* promoters (with their concurrent transcriptional activation) is seen after chronic but not acute cocaine. Interestingly, the levels of H4 and H3 acetylation were found to increase in the NAc shell (not the core) after chronic but not acute cocaine self-administration (190). Epigenetic changes appear to contribute to different components of the addiction trajectory that might serve to uncover new candidates for medications development. Any targeted manipulation of epigenetic marks for therapeutic purposes, however, is presently a distant and challenging prospect.

B. Development

The transition from initial drug exposure to repeated use and subsequently to addiction depends, to a considerable extent, on age and developmental stage. While drug exposure alters brain function, the outcomes of that interaction change as a function of ongoing developmental and aging processes (126, 150). Certain ages and developmental periods (e.g., fetal, childhood, and adolescence) are characterized by broader or more rapid changes than others and, accordingly, exposure to drugs or adverse environmental stimuli during such critical time windows can have dire consequences for normal brain development and addiction vulnerability. A critical factor in the susceptibility of adolescents to risky behaviors, including drug-taking, pertains to the fact that PFC circuitry, which is necessary for self-regulation, is not fully developed until early adulthood (127). The neurobiological underpinnings of this critical transition are not fully understood, but an outline of significant and malleable events during brain development is beginning to emerge.

For example, the protracted period encompassing childhood and adolescence is characterized by increases in white matter volume and organization (195), while cortical gray matter shows a bimodal curve, increasing in volume until the onset of adolescence and then starting to decrease again (127). Brain maturation is also associated with an increased ability to synchronize neural oscillations in several frequency bands (329), and the trajectories of these processes are predictive of brain performance and cognitive abilities (83, 179, 329). Drugs of abuse can perturb these processes, an effect that has been most widely investigated in association with alcohol (139, 307) and cannabis (19, 100, 302) use. Delays in maturation of PFC networks due to drug exposures, genetics, or social deprivation appear to increase risky behaviors in adolescents (including drug-taking). Indeed, brain imaging studies in adolescents have begun to associate abnormalities in PFC function and structure with a higher risk for SUD, consistent with the role of PFC in self-regulation and its disruption as a factor contributing to vulnerability for drug use (170, 216).

C. Social Environment

Epidemiological studies have consistently recognized that environments with a high level of social stressors and poor social support (16, 48, 50, 330) along with easy accessibility to drugs (115, 124, 125) and lack of alternative reinforcers (180) lead to an elevated risk for drug experimentation and addiction. Neuroscientific studies have started to unveil how adverse social environments and lack of opportunities affect the human brain (46) and why early developmental stages may be the most sensitive to such detrimental influences. It is now recognized that brain development is influenced not just by genetic factors but also by environmental exposures (81, 181, 303). Adverse social environments during early childhood have been consistently associated with delayed maturation of prefrontal-limbic connectivity (133). For example, children with a history of early adversity display atypical coupling between amygdala and medial PFC. This abnormal connectivity pattern is partly driven by the actions of the stress hormone cortisol (121) and likely contributes to increased impulsivity (101) and SUD risk (233). The type of persistent social stress that can be triggered by having a subordinate rank among non-human primates (237) or by having poor social support systems in humans (355) has been associated with reduced striatal D2R expression and linked to higher risk for impulsivity and drug use (223, 237, 355). And, as already mentioned, easy access to drugs is an essential contributor to early drug experimentation and repeated consumption (115, 124, 125). Results of both animal (55, 288) and human (60, 309) studies provide compelling evidence that when exposure to drugs occurs during childhood or adolescence it can interfere with developmental brain trajectories, thus exacerbating adverse outcomes (72).

To better ascertain the effects of early drug exposure and the social environment upon developmental brain trajectories, National Institute on Drug Abuse and National Insti-

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tute on Alcohol Abuse and Alcoholism, together with other institutes at the National Institutes of Health, recently launched the Adolescent Brain Cognitive Development (ABCD) study, which will follow over 10,000 youth in the United States as they transition from childhood to adolescence to adulthood, while monitoring their physical and mental health, neurocognition, social environment, substance use, genetic and other biomarkers, and their structural and functional brain development (167).

VI. CLINICAL IMPLICATIONS

A. Prevention

Evidence suggests that prevention of SUDs must include universal components **(TABLE 3)**, including the enhancement of protective factors (e.g., parental support, education) and reverse or reduce risk factors (e.g., deviant behavior, drug abusing peers, social neglect) (10, 148) and should address all forms of drug misuse, including underage use of legal (e.g., tobacco or alcohol), prescription (e.g., stimulant medications), and illicit (230) drugs. Such programs can be implemented in the family, school, and/or community environments.

In addition, tailored prevention interventions should address the specific circumstances of those at higher risk, including people suffering from other mental illnesses or specific disadvantaged conditions. The strengthening of self-control is one example of a promising tailored individual-based intervention. When assessed early in life, poor self-control is a personal characteristic predictive of higher vulnerability for SUD as well as worse physical health, lower economic wealth, and greater criminal involvement (233). Importantly, various training approaches have been identified that can help enhance self-control and other dimensions of executive function when implemented among school-aged children; their usefulness when applied to adults, however, is unclear (116). Effective approaches include enhanced social-emotional and language-literacy programs (283), music education (165), and specific sports programs designed to build individual competences and promote enjoyment (162). A recent summary report paints a promising picture vis á vis the benefits of such interventions for improving self-control circuitry and function as a universal prevention strategy (241). Another promising prevention intervention is the use of mindfulness training to improve self-control, emotional regulation, and stress reactivity, which could also be harnessed for therapeutic purposes (see Ref. 321 and below). An exciting development in prevention research is the recent report that positive parenting (i.e., enhanced supportive parenting style) can overcome the negative effects of childhood poverty on brain development (43). This intervention, a randomized trial of the "Strong African American Families" program among parents and their 11-yr-old children blunted the reductions in specific brain volumes (e.g., left dentate gyrus and CA3 hippocampal subfields and left amygdala) previously associated with childhood poverty (212). This result suggests that enhanced early caregiving (like supportive parenting) could help buffer some of the detrimental effects of adverse social environments (43).

Several studies have also shown that it is possible to target abnormal stress reactivity in children impacted by early adversity and mitigate its impact. For example, studies of children at developmental risk (e.g., in foster care, maltreated, or who suffered parental depression or death) consistently show that psychosocial interventions (e.g., enriched environment, caregiver/parental training) can lower cortisol levels towards the range seen in a low-risk comparison group (304). Similarly, compared with institutional care as usual, high-quality foster care had a positive impact on the integrity of several white matter tracts (27), including those in the external capsule and corpus callosum, whose abnormalities had been associated with neglect-associated emergence of internalizing symptoms in middle childhood or early adolescence (26).

B. Treatment

Medications approved for the treatment of SUD are limited to opioid, nicotine, and alcohol use disorders **(TABLE 4)**.

Table 3. *Prevention matrix*

Risk Factors	Domain	Protective Factors	Reference Nos.
Early aggressive behavior, dysregulated stress response, positive attitudes toward substance use, genetic risk, psychiatric disorder	Individual	Social competence, self-regulatory skills, school readiness, supportive parenting	41, 61, 135, 137, 233, 257, 258, 301
Harsh or absent parenting	Family	Positive parenting	42, 248
Antisocial influence	Peer	Positive peer networks	305
Poor classroom management, poor control of drug availability	School	Positive school environment, teacher behavior management competence	20, 110, 177, 191
Laws, policies, and perceived norms for substance use	Community	Community-level strategies to prevent substance use	44, 141

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Table 4. *Current FDA-approved pharmacological treatments for SUD*

SUD	Current Status	FDA-Approved Medication	Promising Targets	Reference Nos.
Opioids (OUD)	Mu opioid receptor (MOR) drugs with different properties have been approved by the FDA and are recommended as first-line interventions, supported by high-quality evidence. Despite their effectiveness, relapse rates are very high (50% within 6 mo). α-Adrenergic agonists for opioid withdrawal.	Maintenance medications: buprenorphine (partial agonist), methadone (full agonist), naltrexone (antagonist). Reverse opioid overdoses: naloxone. Control opioid withdrawal: lofexidine.		93, 134, 353
Nicotine	There are FDA-approved pharmacotherapies for smoking cessation. Despite their effectiveness, relapse rates are very high (75% within 1 yr).	Nicotine replacement therapies: patches, oral and nasal sprays, inhalers, and lozenges. Bupropion, varenicline.	Nortriptyline, clonidine	131, 265
Alcohol (AUD)	There are three FDA-approved medications for the treatment of AUD, displaying different mechanisms of action.	Disulfiram is an ADH inhibitor that blocks the breakdown of alcohol leading to a buildup of acetaldehyde that results in unpleasant side effects. Naltrexone is a MOR and KOR antagonist that reduces the pleasure a person with AUD can experience while drinking. Acamprosate is an NMDA receptor function booster that appears to reduce or stop severe alcohol withdrawal symptoms during detoxification.	Anticonvulsants: gabapentin, topiramate, and pregabalin. Antipsychotics: quetiapine and aripiprazole. Antidepressants: duloxetine and venlafaxine. Others: baclofen, ondansetron, and nalmefene.	4
Stimulants	No FDA-approved medications		NMDAR antagonist ketamine, A2AR antagonists, 5-HT_{2C}R agonist lorcaserin, *N*-acetylcysteine, D3R antagonists, cannabidiol	14, 71, 163
Cannabis (CUD)	No FDA-approved medications		CB1R agonists, gabapentin, *N*-acetylcysteine, FAAH inhibitors	132, 280

Current United States Food and Drug Administration (FDA)-approved pharmacological treatments for substance use disorder (SUD) and other promising medications chosen based on reproducible preclinical findings that interfered with drug consumption, prevented relapse, or inhibited craving and/or on pilot clinical studies showing positive results in interfering with subjective drug reward, drug consumption, reducing craving, or withdrawal.

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There are several promising candidates for the treatment of stimulant and OUD that are undergoing clinical trials (see Supplementary TABLE 2; https://github.com/rubenbaler/PRV-00014-2018R1/blob/master/ST.2.docx), although for the most part research is still at the preclinical stages. On the other hand, the characterization of the various neuronal circuits disrupted in addiction identifies them as suitable targets for personalized interventions. For example, strengthening of self-control fronto-cortical circuitry might help prevent relapse (130, 320). The amygdala/hippocampus (mediating emotions, mood, and stress reactivity) and the insula (responsible for integrating and translating interoceptive signals) are also relevant as targets for addiction treatment (246, 339).

These could be translated into the next generation of nonmedication-based interventions (i.e., targeted behavioral training, noninvasive modulation) designed to increase the effectiveness of control networks as a way to treat addiction, even among those without intention to quit (320). By the same token, TMS or tDCS could prove helpful in reducing craving by modulating insular activity (BOXES 3 and 4). Finally, there is experimental evidence suggesting that mindfulness-based techniques may positively impact cognitive processes (319) and mitigate addictive behaviors (97, 200, 321, 358). Indeed, preliminary imaging data showing that mindfulness activated the amygdala, striatum, ACC, PFC, and insula, which are regions that modulate emotion, self-regulation, and interoception, highlight its potential promise in addiction treatment (319).

VII. CONCLUSIONS

Significant advances in neuroscience have given us an understanding of the effects of drugs in the brain that result in addiction, which have led to the recognition that addiction is a chronic brain disorder that should be treated as done for any other medical condition. Similarly, our increased understanding of the neurobiological processes that are associated with vulnerability for drug experimentation and SUD, including the effects of exposure to adverse environmental conditions, is helping redefine our thinking around tailored prevention interventions for at-risk individuals. However, much work is still needed to capture the complexity of the effects of drugs and other rewards in our brains, to understand how they interact, and how they ultimately motivate behavior.

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Address for reprint requests and other correspondence: N. D. Volkow, NSC Bldg., Rm. 5274, MS 9581, 6001 Executive Blvd., Rockville, MD 20852 (e-mail: nvolkow@nida.nih.gov).

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