Addiction: Beyond dopamine reward circuitry

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Dopamine (DA) is considered crucial for the rewarding effects of drugs of abuse, but its role in addiction is much less clear. This review focuses on studies that used PET to characterize the brain DA system in addicted subjects. These studies have corroborated in humans the relevance of drug-induced fast DA increases in striatum [including nucleus accumbens (NAc)] in their rewarding effects but have unexpectedly shown that in addicted subjects, drug-induced DA increases (as well as their subjective reinforcing effects) are markedly blunted compared with controls. In contrast, addicted subjects show significant DA increases in striatum in response to drug-conditioned cues that are associated with self-reports of drug craving and appear to be of a greater magnitude than the DA responses to the drug. We postulate that the discrepancy between the expectation for the drug effects (conditioned responses) and the blunted pharmacological effects maintains drug taking in an attempt to achieve the expected reward. Also, whether tested during early or protracted withdrawal, addicted subjects show lower levels of D2 receptors in striatum (including NAc), which are associated with decreases in baseline activity in frontal brain regions implicated in salience attribution (orbitofrontal cortex) and inhibitory control (anterior cingulate gyrus), whose disruption results in compulsivity and impulsivity. These results point to an imbalance between dopaminergic circuits that underlie reward and conditioning and those that underlie executive function (emotional control and decision making), which we postulate contributes to the compulsive drug use and loss of control in addiction.

prefrontal cortex | dorsal striatum | substance use disorders | stimulant drugs | brain imaging

Drugs of abuse (including alcohol) are inherently rewarding, which is why they are consumed by humans or self-administered by laboratory animals (1). Only a small percentage of individuals exposed to drugs will become addicted, that is, shift from controlled drug use to compulsive drug use with loss of control over intake despite adverse consequences, however (2). Factors that determine who becomes addicted include genetic (50% of risk), developmental (risk is higher in adolescence), and environmental (e.g., drug access, stress) factors (2).

The mesolimbic dopamine (DA) pathway [DA cells in ventral tegmental area (VTA) projecting into nucleus accumbens (NAc)] seems to be crucial for drug reward (1). Other DA pathways [mesostriatal (DA cells in substantia nigra {SN} projecting into dorsal striatum) and mesocortical (DA cells in VTA projecting into frontal cortex)] are now also recognized to contribute to drug reward and addiction (1). The mode of DA cell firing also differentially modulates the rewarding and conditioning effects, of drugs (predominantly phasic DA cell firing) vs. the changes in executive function that occur in addiction (predominantly tonic DA cell firing) (3, 4).

This review summarizes studies that used PET to evaluate DA's role in drug reward and addiction. These findings show that addiction affects not only the DA reward circuit but circuits involved with conditioning/habits, motivation, and executive functions (inhibitory control, salience attribution, and decision making). Other neurotransmitters (and neuropeptides) are involved with drug reward (i.e., cannabinoids, opioids) and with the neuroadaptations from repeated drug use (i.e., glutamate, opioids, GABA, corticotropic-releasing factor). These are not discussed here (except for glutamate), but several reviews address them (5, 6).

DA and Acute Drug Reward

All drugs that can lead to addiction increase DA in NAc, which is achieved through their interaction with different molecular targets by the various drug classes (6) (Table 1). In humans, PET studies have shown that several drugs [stimulants (7, 8), nicotine (9), alcohol (10), and marijuana (11)] increase DA in dorsal and ventral striatum (where NAc is located). These studies used a radiotracer that binds to DA D2 receptors (D2Rs) but only when these are not occupied by DA (i.e., [^{11}C]raclopride). By comparing binding after placebo and after the drug, these studies estimate the decreases in D2R availability induced by the drug, which are proportional to DA increases (12). Most studies have reported that participants who display the greatest DA increases with the drug also report the most intense "high" or "euphoria" (reviewed ref. 13).

PET studies have also shown that the speed with which a drug enters and leaves the brain (pharmacokinetic profile) is crucial for its reinforcing effects. Specifically, PET studies of brain pharmacokinetics of drugs labeled with positron emitters show that peak levels in human brain are reached within 10 min after i.v. administration and that this fast drug uptake is associated with the high (13) (Fig. 1). Indeed, for an equivalent level of cocaine reaching the brain (assessed as equivalent level of DA transporter blockade), when cocaine entered the brain rapidly (smoked and i.v. administration), it elicited a more intense high than when it entered the brain more slowly (snorted) (14). This is consistent with preclinical studies showing that the faster the drug's entry into the brain, the stronger are its reinforcing effects (15). This probably reflects the fact that abrupt and large DA increases triggered by drugs mimic the fast and large DA increases associated with phasic DA firing that are associated in the brain with conveying information about reward and saliency (16).

Drug-induced DA increases in NAc occur in nonaddicted as well as addicted subjects, which raises the question of how they relate to addiction.

To start with, there is increasing evidence that DA's role in reinforcement is more complex than just coding for reward per se (hedonic pleasure) and that stimuli that induce fast and large DA increases also trigger conditioned responses and elicit incentive motivation to procure them (17). Through conditioning, a neutral stimulus that is linked with the reinforcer (i.e., natural reinforcer, drug) acquires the ability by

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Table 1. Main classes of drugs of abuse, their main molecular targets, and some of the mechanism(s) by which they increase DA in NAc (44)

Drug	Target	Mechanism for DA increases
Stimulant drugs (cocaine, amphetamine, methamphetamine)	DAT	Blocks DAT on the terminals of DA projecting neurons from VTA to NAc (cocaine) or releases DA from the vesicles of DA terminals (methamphetamine, amphetamine)
Opioids (heroin, opioid analgesics)	MOR	Disinhibits VTA DA neurons by inhibiting GABA interneurons that contain MOR in the VTA or directly activates NAc neurons that contain MOR
Nicotine (cigarettes and other tobacco products)	Nicotinic receptors (predominantly $\alpha4\beta2$ subtype)	Directly activates VTA DA neurons by stimulating their nicotine receptors and indirectly activates them by stimulating the nicotine receptors in glutamatergic terminals to VTA DA neurons
Alcohol and inhalants	Multiple targets, including GABA and glutamate receptors	Facilitates GABAergic neurotransmission, which may disinhibit VTA DA neurons from GABA interneurons or may inhibit glutamate terminals that regulate DA release in Nac
Cannabinoids (marihuana)	Cannabinoid CB1 receptors	Regulates dopaminergic signaling through CB1R in NAc neurons and in GABA and glutamate terminals to NAc

DAT, DA transporter; MOR, μ-opioid receptor.

itself to increase DA in striatum (including NAc) in anticipation of the reward, and this is associated with drug seeking (17). In animals trained to expect a natural reinforcer (food) when exposed to a conditioned stimulus (CS), the DA neurons stop responding to the primary reinforcer and, instead, respond to the CS (16). The extent to which a similar process occurs in response to drugs of abuse is unclear, however, because drugs, through their pharmacological actions, can directly activate DA neurons

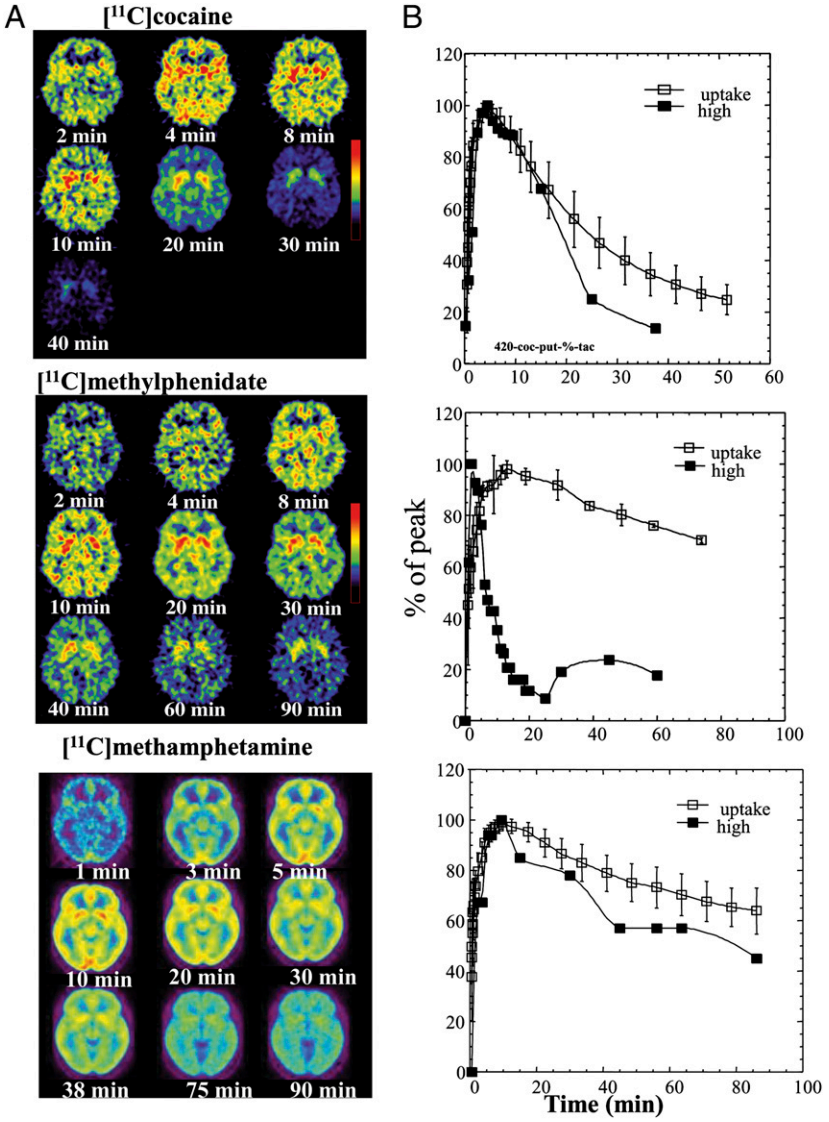

Fig. 1. Pharmacokinetics of stimulant drugs in the human brain and relationship to the "high." (*A*) Axial brain images of the distribution of [^{11}C]cocaine, [^{11}C]MP, and [^{11}C]methamphetamine at different times (minutes) after its administration. (*B*) Time activity curve for the concentration of [^{11}C]cocaine, [^{11}C]MP, and [^{11}C]methamphetamine in striatum alongside the temporal course for the high experienced after i.v. administration of these drugs. Note that the fast brain uptake for these drugs corresponds to the temporal course of the high, which suggests that the high is associated with the "rate of DA increases." In contrast, their clearance shows a correspondence with the high for cocaine and for methamphetamine but not for MP. The difference between MP and cocaine may reflect the differences in their rate of clearance and that between MP and methamphetamine may reflect their different mechanisms of action. Specifically, because MP and cocaine increase DA by blocking DA transporters, the DA increases are terminated by autoreceptor activation, which inhibits DA release. For cocaine, its fast rate of clearance (20-min half-life in brain) results in short-lasting autoreceptor activation, whereas for MP, its slower clearance (60-min half-life) results in long-lasting inhibition of DA release by autoreceptors, which terminates the high even though the drug is still in the brain. In contrast, methamphetamine, which is a DA releaser, is not sensitive to autoreceptor activation; thus, DA increases are not terminated by this mechanism, accounting for the longer lasting duration of the high. Modified from ref. 18. Copyright (1995) American Medical Association. All rights reserved. Reprinted from ref. 43. Copyright (2008), with permission from Elsevier.

(i.e., nicotine) or increase DA release (i.e., amphetamine) (Table 1).

To answer this, we compared DA increases induced by the stimulant drug methylphenidate (MP) between cocaine-addicted subjects and controls. Like cocaine, MP increases DA by blocking DA transporters; both drugs have a similar distribution in human brain and have similar behavioral effects when given i.v. (18). In detoxified cocaine-addicted subjects (n = 20, detoxified 3–6 wk), we showed marked attenuation of MP-induced DA increases in striatum (50% lower) and of the increases in self-reports of high, compared with non–drug-abusing controls (n = 23). Similar findings were reported after administration of i.v. amphetamine (another stimulant drug) in recently detoxified cocaine abusers (detoxified 2 wk), who also showed decreased DA release in striatum and attenuated self-reports of euphoria (19). Because a confound in these studies was the possibility that drug withdrawal accounted for the attenuated DA responses, we repeated this study in active cocaine-addicted subjects (n = 19, nondetoxified) (20). In active cocaine abusers, MP-induced DA changes did not differ from placebo and the DA changes were 80% lower than in controls (n = 24); the self-reports of high were also attenuated (Fig. 2). Marked blunting of striatal DA increases secondary to MP or to amphetamine has also been documented in detoxified alcoholics (reviewed in ref. 13). If, as is currently believed, drug-induced DA increases in NAc underlie drug reward, why would cocaine-addicted subjects, who show a marked attenuation of drug-induced DA increases, compulsively take the drug?

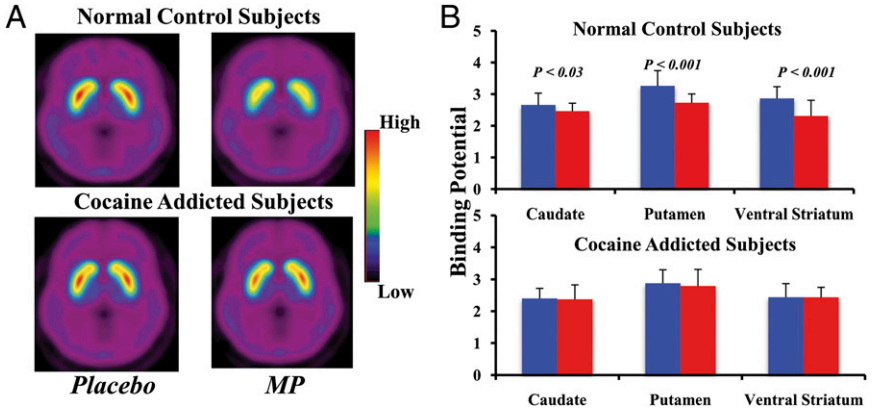

Fig. 2. DA changes induced by i.v. MP in controls and in active cocaine-addicted subjects. (*A*) Average nondisplaceable biding potential (BP_{ND}) images of [^{11}C]raclopride in active cocaine-addicted subjects (n = 19) and in controls (n = 24) tested after placebo and after i.v. MP. (*B*) D2R availability (BP_{ND}) in caudate, putamen, and ventral striatum after placebo (blue) and after MP (red) in controls and in cocaine-addicted subjects. MP reduced D2R in controls but not in cocaine-addicted subjects. Note that cocaine abusers show both decreases in baseline striatal D2R availability (placebo measure) and decreases in DA release when given i.v. MP (measured as decreases in D2R availability from baseline). Although one could question the extent to which the low striatal D2R availability in cocaine-addicted subject limits the ability to detect further decreases from MP, the fact that cocaine-addicted subjects show reductions in D2R availability when exposed to cocaine cues (Fig. 3) indicates that the attenuated effects of MP on [^{11}C] raclopride binding reflect decreased DA release.

DA and Conditioning to Drug Cues

The explanation may arise from the process of conditioning, which is one of the initial neuroadaptations that follow exposure to drugs and involves DA phasic signaling (predominantly D1Rs) and synaptic changes in NMDA and AMPA receptors (modulated by glutamate) (21, 22). These conditioned responses are believed to underlie the intense desire for the drug (craving) and the compulsive use that occurs when addicted subjects are exposed to drug cues.

To assess if drug conditioned cues would increase DA in cocaine-addicted subjects, we tested active cocaine-addicted subjects (n = 18) when subjects watched a neutral video (nature scenes) vs. when they watched a cocaine-cue video (scenes of subjects procuring and smoking cocaine) (23). Cocaine cues significantly increased DA in dorsal striatum, and the magnitude of this increase was correlated with the subjective experience of craving (Fig. 3); similar findings were reported by another laboratory (24). Subjects with the largest cue-induced DA increases in dorsal striatum also had the highest scores on measures of addiction severity. Because the dorsal striatum is implicated in habit learning, this association is likely to reflect the strengthening of habits as chronicity of addiction progresses. This suggests that a basic disruption in addiction might be DA-triggered conditioned responses that result in habits leading to compulsive drug consumption. Inasmuch as in cocaine-addicted subjects, the DA increases triggered by conditioned cues appear to be larger than those produced by a stimulant drug, this suggests that conditioned responses may drive the DA signaling that triggers and maintains the motivation to take the drug. To the extent that the drug (even when its DA-enhancing effects are attenuated) predicts reward, the act of its administration (e.g., injection, smoking) may become a conditioned cue and, as such, may increase DA. Thus, although drugs may initially lead to DA release in striatum (signaling reward), with repeated administration and as habits develop, there appears to be a shift in the DA increases from the drug to the CS, as reported for

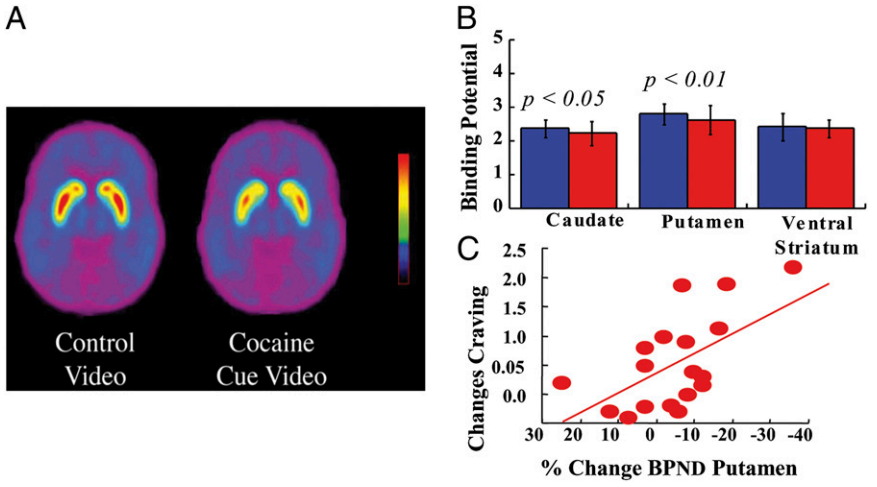

Fig. 3. DA changes induced by conditioned cues in active cocaine-addicted subjects. (*A*) Average nondisplaceable biding potential (BP_{ND}) images of [^{11}C]raclopride in cocaine-addicted subjects (n = 17) tested while viewing a neutral video (nature scenes) and while viewing a cocaine-cues video (subjects administering cocaine). (*B*) D2R availability (BP_{ND}) in caudate, putamen, and ventral striatum for the neutral video (blue) and the cocaine-cues video (red). The cocaine cues decreased D2R in caudate and putamen. (*C*) Correlations between changes in D2R (reflecting DA increases) and self-reports of cocaine craving induced by the cocaine-cues video. Modified from ref. 23.

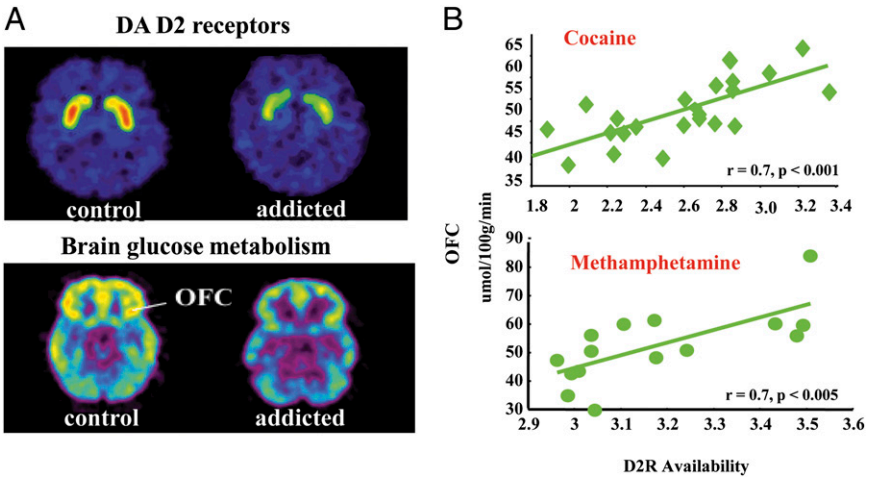

Fig. 4. Correlations between striatal D2R availability and metabolism in prefrontal brain regions. (*A*) Axial brain images for a control and for a cocaine-addicted subject for baseline images of D2R availability in striatum (obtained with [^{11}C]raclopride) and of brain glucose metabolism in OFC (obtained with [^{18}F]FDG). (*B*) Correlations between striatal D2R and metabolism in OFC in cocaine-addicted and methamphetamine-addicted subjects. Reprinted from ref. 13, Copyright (2009), with permission from Elsevier.

natural reinforcers (16). Preclinical studies have revealed that glutamatergic projections from prefrontal cortex into VTA/SN and NAc mediate these conditioned responses (5).

DA and Inhibitory Control in Addiction

The capacity to inhibit prepotent responses is likely to contribute to an individual's ability to restrain from taking drugs, and thus his or her vulnerability to addiction (25).

PET studies have shown that addicted subjects have significant reductions in D2R availability in striatum that persist months after protracted detoxification (reviewed in ref. 13). To investigate the functional significance of the striatal D2R reductions, we have assessed their relationship to baseline measures of brain glucose metabolism (marker of brain function). We have shown that reductions in striatal D2R are associated with decreased metabolism in orbitofrontal cortex (OFC), anterior cingulate gyrus (ACC), and dorsolateral prefrontal cortex (DLPFC) (26–28) (Fig. 4). Because OFC, CG, and DLPFC are involved with salience attribution, inhibitory control/emotion regulation, and decision making, we had postulated that their improper regulation by DA in addicted subjects could underlie the enhanced motivational value of drugs in their behavior and loss of control over drug intake (29). In addition, because impairments in OFC and ACC are associated with compulsive behaviors and impulsivity, we postulated that DA's impaired modulation of these regions could underlie the compulsive and impulsive drug intake seen in addiction (30, 31). Indeed, in methamphetamine abusers, low striatal D2R was

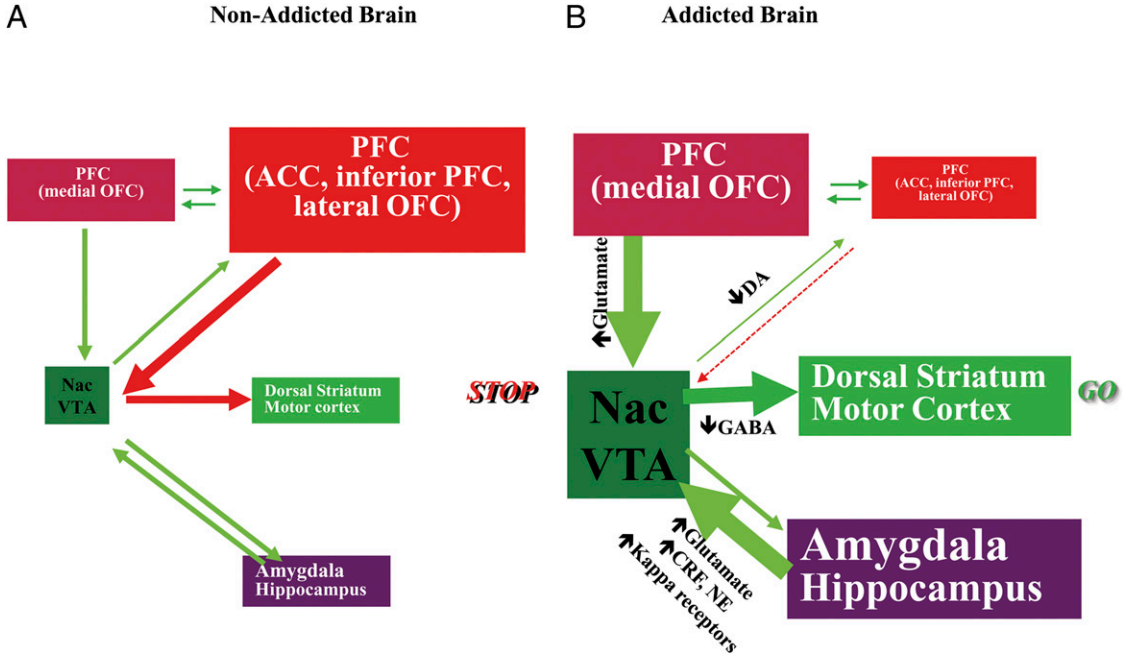

Fig. 5. Model proposing a network of interacting circuits underlying addiction: reward (nucleus accumbens, VTA, and ventral pallidum), conditioning/memory (amygdala, medial OFC for attribution of saliency, hippocampus, and dorsal striatum for habits), executive control (DLPFC, ACC, inferior frontal cortex, and lateral OFC), and motivation/drive (medial OFC for attribution of saliency, ventral ACC, VTA, SN, dorsal striatum, and motor cortex). Nac, nucleus accumbens. (*A*) When these circuits are balanced, this results in proper inhibitory control and decision making. (*B*) During addiction, when the enhanced expectation value of the drug in the reward, motivation, and memory circuits overcomes the control circuit, this favors a positive-feedback loop initiated by the consumption of the drug and perpetuated by the enhanced activation of the motivation/drive and memory circuits. These circuits also interact with circuits involved in mood regulation, including stress reactivity (which involves the amygdala and hypothalamus) and interoception (which involves the insula and ACC and contributes to awareness of craving). Several neurotransmitters are implicated in these neuroadaptations, including glutamate, GABA, norepinephrine, corticotropic-releasing factor, and opioid receptors. CRF, corticotropic-releasing factor; NE, norepinephrine. Modified with permission from ref. 35; permission conveyed through Copyright Clearance Center, Inc.

associated with impulsivity (32), and low striatal D2R was associated with impulsivity and predicted compulsive cocaine administration in rodents (33).

It is also possible that the initial vulnerability for drug use occurs in prefrontal regions and that repeated drug use triggers the decreases in striatal D2R. Indeed, in a study done in subjects who, despite having a high risk for alcoholism (positive family history of alcoholism), were not alcoholics, we showed higher than normal striatal D2R availability that was associated with normal metabolism in OFC, ACC, and DLPFC (25). We interpreted this to suggest that normal prefrontal function may have protected these subjects from alcohol abuse.

DA and Motivation in Addiction

DA is also involved in motivation (i.e., vigor, persistence, effort toward the pursuit of reinforcing stimuli) through its regulation of several target regions, including NAc, ACC, OFC, DLPFC, amygdala, dorsal striatum, and ventral pallidum (34).

The enhanced motivation to procure drugs is a hallmark of addiction. Drug-addicted individuals will go to extreme behaviors to obtain drugs, even at the expense of seriously adverse consequences (2). Drug seeking and drug taking become their main motivational drives, which displace other activities (35). Thus, the addicted subject is aroused and motivated when seeking to procure the drug but tends to be withdrawn and apathetic when exposed to non–drug-related activities. This shift has been studied by comparing the brain activation patterns occurring with exposure to conditioned cues with those occurring without such cues.

In contrast to the decreases in prefrontal activity reported in detoxified cocaine abusers when not stimulated with drug or drug cues (reviewed in ref. 13), these prefrontal regions become activated when cocaine abusers are exposed to craving-inducing stimuli (either drugs or cues) (36–39). Similarly, cocaine abusers studied shortly after an episode of cocaine binging showed increased metabolic activity in OFC and ACC (also dorsal striatum) that was associated with craving (40).

Moreover, when we compared the response to i.v. MP between cocaine-addicted and nonaddicted subjects, we showed that MP increased metabolism in ventral ACC and medial OFC (an effect associated with craving) only in addicted subjects, whereas it decreased metabolism in these regions in nonaddicted subjects (41). This suggests that the activation of these prefrontal regions with drug exposure may be specific to addiction and associated with the enhanced desire for the drug. Moreover, in a subsequent study in which we prompted cocaine-addicted subjects to inhibit craving purposefully when exposed to drug cues, we showed that subjects who were successful in inhibiting craving decreased metabolism in medial OFC (processes motivational value of reinforcer) and NAc (predicts reward) (42).

These findings corroborate the involvement of OFC, ACC, and striatum in the enhanced motivation to procure the drug in addiction.

Systems Model of Addiction

As summarized above, several brain circuits are relevant in the neurobiology of addiction. Here, we highlighted four of these circuits: reward/saliency, motivation/drive, conditioning/habits, and inhibitory control/executive function (Fig. 5). The mood regulation circuit (contributes to regulation of stress reactivity) and the interoception circuit (contributes to awareness of drug craving and mood) also participate in addiction, but their involvement in the human brain has been much less investigated. Consequences of the disruption of these circuits are an enhanced motivational value of the drug (secondary to learned associations through conditioning and habits) at the expense of other reinforcers (secondary to decreased sensitivity of the reward circuit) and an impaired ability to inhibit the intentional actions associated with the strong desire to take the drug (secondary to impaired executive function) that result in compulsive drug taking in addiction (35).

Although it is likely that DA changes underlie some aberrant behaviors in addiction, it is also possible that some DA changes may reflect attempts to compensate for deficits in other neurotransmitters, particularly because DA is modulated by glutamate (GABA has been less investigated). Corticostriatal glutamatergic terminals are responsible for learning well-established behaviors and for changing these behaviors when they are no longer adaptive, and neuroadaptations in these projections (and in amygdalostriatal glutamate pathways) with repeated drug use (including impaired regulation of glutamate synaptic release) are implicated in the enhanced motivation for drug seeking that occurs in addiction (5). Impairments in glutamate-induced neuroplasticity with chronic drug exposure are also likely to be involved in the prefrontal function deficits reported in addicted individuals that result in impairments in inhibitory control and in inability to change maladaptive behaviors and to learn from the adverse consequences of drug use.

This model suggests a multipronged therapeutical approach to addiction to decrease the reinforcing properties of drugs, enhance the rewarding properties of natural reinforcers, inhibit conditioned-learned associations, enhance motivation for non–drug-related activities, and strengthen inhibitory control.

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