

The neurocircuitry of illicit psychostimulant addiction: acute and chronic effects in humans

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Abstract: Illicit psychostimulant addiction remains a significant problem worldwide, despite decades of research into the neural underpinnings and various treatment approaches. The purpose of this review is to provide a succinct overview of the neurocircuitry involved in drug addiction, as well as the acute and chronic effects of cocaine and amphetamines within this circuitry in humans. Investigational pharmacological treatments for illicit psychostimulant addiction are also reviewed. Our current knowledge base clearly demonstrates that illicit psychostimulants produce lasting adaptive neural and behavioral changes that contribute to the progression and maintenance of addiction. However, attempts at generating pharmacological treatments for psychostimulant addiction have historically focused on intervening at the level of the acute effects of these drugs. The lack of approved pharmacological treatments for psychostimulant addiction highlights the need for new treatment strategies, especially those that prevent or ameliorate the adaptive neural, cognitive, and behavioral changes caused by chronic use of this class of illicit drugs.

Keywords: substance abuse, pharmacotherapy, cocaine, amphetamine, methamphetamine, addiction, human

Introduction

Drug addiction, also referred to as substance dependence, is a serious and chronically relapsing disease wherein the afflicted individual has difficulty limiting drug intake, exhibits high motivation to take the drug, continues using the drug despite negative consequences, and experiences negative emotional and physiological states when the drug is withheld.¹ In the United States, the 2010 prevalence rates (current and past-month use, in persons aged 12 years or older) for illicit drug use (including marijuana, cocaine, and heroin) reached 22.6 million (8.9%).² The estimated number of persons aged 12 years or older classified with substance dependence (including illicit drugs and alcohol) in 2010 was 22.1 million, representing 8.7% of the US population.² Furthermore, 20.5 million Americans were classified as needing treatment for an illicit drug or alcohol use problem.² Of the 1 million persons that felt that they needed treatment for illicit drug or alcohol use problems, only 33% made an effort to seek treatment.² These surprisingly high numbers and lack of effort to seek treatment clearly indicate that illicit drug addiction remains a significant problem in the US.

The most frequently abused illicit psychostimulants include cocaine and amphetamines, the latter of which represents a class of structurally related molecules, including D-amphetamine (AMPH), methamphetamine (METH), and 3,4-methylenedioxymethamphetamine (MDMA, commonly referred to as Ecstasy).

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Recent epidemiological data showed that in 2010 there were 1.5 million current cocaine users aged 12 or older, which comprised 0.6% of the population.² The number of METH users represented 0.1% of the population, and the number of MDMA users was approximately 0.5%.² In addition to the use of these classical illicit psychostimulants, the years 2010 and 2011 were characterized by a dramatic rise in the number of users of a newer class of amphetamine-like psychostimulants called synthetic cathinones, more frequently referred to as “bath salts”.³ However, due to the very recent emergence of the use of synthetic cathinones, national epidemiological data on the prevalence of their use as well as long-term effects on the brain are not yet available.

Using both animal models of addiction as well as advanced neuroimaging techniques, researchers have identified various neural substrates of addiction to psychostimulants, with primary emphasis on the ability of addictive drugs to “hijack” the brain’s natural reward circuitry.⁴ In recent years, it has become apparent that while acute psychostimulant use activates this reward circuitry, chronic drug use progressively “rewires” the brain and produces many lasting neuroadaptations that have been characterized as a pathology of “staged neuroplasticity.”⁵ The present review will provide a general overview of the reward and addiction neurocircuitries, the initial subjective effects of illicit psychostimulants and their mechanisms of action, the neuropsychological, psychiatric, and neurological sequelae of chronic psychostimulant use in humans, and functional and structural changes in the neurocircuitry of addiction. Since MDMA and synthetic cathinones possess unique pharmacological and hallucinogenic properties, and their addictive potential is less well established, our review will focus on the traditional psychostimulants cocaine, AMPH, and METH. In light of the fact that no pharmacological treatment has yet been approved by the US Food and Drug Administration (FDA) specifically for psychostimulant dependence, we will also summarize the newer and more promising investigational treatments and approaches.

Theories of addiction

The transition from drug use to drug dependence is impacted by numerous factors, including genetics, environmental influences (such as stress and early life experiences), and neurochemical and neuroanatomical modifications in the brain that result from repeated drug use.^{6,7} Initial drug use can be attributed to the ability of the drug to act as a reward (ie, a pleasurable emotional state or positive reinforcer), which can lead to repeated drug use and dependence.^{8,9} A great deal of research has focused on the molecular and

neuroanatomical mechanisms of the initial rewarding or reinforcing effect of drugs of abuse. However, more recent research on the long-term neuroanatomical and molecular changes in the brain that result from chronic drug use has revealed drug addiction to be highly complex and involve brain systems beyond the canonical reward circuitry.

Several parallel and intersecting theories of drug addiction include changes in behavior that are supported by various alterations in the underlying neurocircuitry of addiction. Robinson and Berridge hypothesized that repeated drug use produces alterations in the brain reward and associative learning systems, such that the drug user becomes increasingly sensitive to both the drug and drug-associated cues, resulting in pathological drug seeking or “wanting.”^{10,11} Koob and Le Moal have postulated that repeated drug use and dependence are a result of decreased functioning of the brain’s reward system coupled with an increase in the engagement of the brain’s antireward or stress circuitries.^{12,13} These two opposing neurocircuitries are hypothesized to interact in a cyclical manner that ultimately manifests as addiction.¹² Everitt and Robbins have theorized that drug addiction is the result of transitions from initial, voluntary drug use to habitual and eventually compulsive drug use, which results from a switch in the relative engagement of the neurocircuitries underlying these behaviors.¹⁴ Finally, Hyman and colleagues have also suggested that addiction is a disorder characterized by the “hijacking” of normal learning and memory processes involved in reward seeking and drug–cue associations.⁴

These theories all agree that drug addiction is characterized by a progression or shift from initial stages, where the drug user is in control, to the end stages, where the drug user has lost control over drug use. Furthermore, this continuum of behavioral adaptation is proposed to be mediated by drug-induced alterations in the neurocircuitries underlying reward, executive function, and learning and memory. Despite these recent advances in our understanding of the addicted brain, the majority of FDA-approved treatments for drug addiction aim to intervene at the level of the acute rewarding effects of drugs of abuse.

The neurocircuitry of addiction

The brain reward circuitry underlies all motivated behavior for natural rewards (eg, food, water, and sex) as well as drug rewards. Some of the key brain regions of the reward circuitry include the ventral tegmental area (VTA), nucleus accumbens (NAc), prefrontal cortex (PFC), basal ganglia, dorsal striatum (DS), amygdala (AMG), and hippocampus (HPC) (Figure 1).

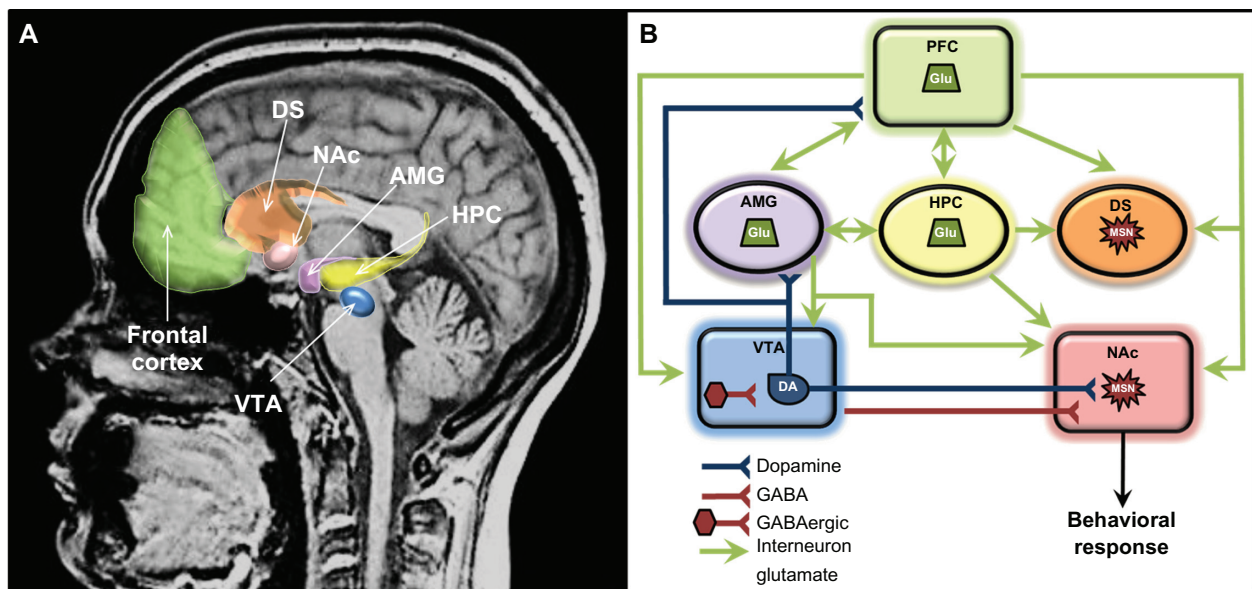


Figure 1 (A and B) Components of the principal reward neurocircuitries in the brain. **(A)** Neuroanatomical location of reward circuitry; **(B)** schematic of reward circuitry with primary neurotransmitter projections.

Note: Frontal cortex includes prefrontal, orbitofrontal, and anterior cingulate cortex.

Abbreviations: AMG, amygdala; DA, dopaminergic neurons; DS, dorsal striatum; GABA, γ -aminobutyric acid; Glu, glutamatergic neurons; HPC, hippocampus; MSN, medium spiny neurons; NAc, nucleus accumbens; PFC, prefrontal cortex; VTA, ventral tegmental area.

The rewarding effects of drugs and the progression from initial drug use to dependence are highly dependent on complex interactions between and adaptations within these regions. The key neurotransmitter that has been historically thought to mediate reward is dopamine (DA). However, as discussed below, psychostimulants also increase extracellular levels of glutamate (Glu), norepinephrine (NE), serotonin (5-HT), and other neurotransmitters within this neurocircuitry, which contribute to many of the long-term molecular and behavioral changes underlying addiction.^{15,16}

Reward systems

Ventral tegmental area

The brain reward circuit functionally begins with the VTA, which contains a cluster of dopaminergic cells with efferent projections to the NAc and to other brain regions, such as the PFC and AMG. Many natural rewards and drugs of abuse activate the dopaminergic neurons of the VTA to release DA in these brain regions.^{10,17–20} The VTA is also modulated by glutamatergic inputs from the PFC and AMG, in addition to a subpopulation of inhibitory γ -aminobutyric acid (GABA), interneurons within the VTA.²¹ Recent evidence also suggests that inputs to the VTA containing the stress-related peptide corticotropin releasing factor (CRF) may be responsible for modulating stress-induced influences on drug-seeking behavior, while orexin-containing inputs to the VTA from hypothalamic regions may also be involved

in relapse-like behaviors.^{22,23} These neurotransmitter and neuropeptide interactions result in numerous cellular and molecular changes that contribute to reward-associated learning and the development of addiction.²⁴

Nucleus accumbens

Most drugs of abuse, particularly psychostimulants, induce DA release at the level of the terminal fields in the NAc, PFC, and AMG.²⁵ The release of DA in the NAc appears to be crucial for the rewarding effects of drugs of abuse. The NAc, which is contained within the ventral striatum, is composed primarily of GABAergic medium spiny neurons (MSNs). The NAc can be functionally subdivided into two distinct subregions, the core and shell, which respond to rewarding stimuli differently and are thought to mediate distinct aspects of addictive processes. The release of DA in the NAc shell contributes to the initial rewarding and reinforcing effects of drugs and the assignment of salience to rewarding stimuli, whereas DA release in the NAc core is thought to be more associated with the expression of learned behaviors in response to rewarding stimuli, such as drug seeking.^{26–30} Drug-induced elevations in extracellular DA in the NAc and other brain regions of the reward circuitry are modulated by numerous other neurotransmitter systems, including GABA, Glu, endogenous opioids and cannabinoids, 5-HT, NE, and various neuropeptides such as CRF.^{15,16,25,31–33} Furthermore, these neurotransmitter systems

can modulate psychostimulant intake and drug-seeking behavior. For example, various ionotropic and metabotropic glutamate receptors in both the NAc core and shell mediate context-induced reinstatement of cocaine seeking.³⁴

Executive function and habit systems

Prefrontal cortex

The PFC is a key regulator of cognitive and emotional processes, and contains many functionally distinct subregions. The dorsolateral PFC, orbitofrontal cortex (OFC), and anterior cingulate cortex are involved in salience attribution, decision-making, inhibition of inappropriate behaviors, behavioral and cognitive flexibility, and the regulation of emotion.^{35–37} These regions of the PFC have dense populations of glutamatergic cell bodies with efferent pathways that synapse onto the same cell populations (ie, MSNs) in the NAc that receive dopaminergic afferents from the VTA.³⁸ In addition, glutamatergic efferents from the PFC also project to the AMG, VTA, DS, and indirectly to the HPC.^{39–41} Thus, the PFC is situated to modulate the rewarding effects of drugs of abuse and drug-seeking behavior, as well as relapse to drug taking.⁴² The PFC coordinates the flexibility with which an organism adapts its goal-directed behavior at many stages in the addiction process, and is modulated by inputs from other cortical and subcortical regions.

Dorsal striatum and cortical-basal ganglia loops

Regions of the basal ganglia, which include the dorsal and ventral striatum, internal and external segments of the globus pallidus, subthalamic nucleus, and dopaminergic cell bodies in the substantia nigra, are highly implicated not only in fine motor control but also in PFC function.⁴³ Of these regions, the NAc (described above) and the DS (described below) are most frequently examined with respect to addiction. Thus, only a brief description of the modulatory role of the basal ganglia in addiction-relevant circuits will be mentioned here. The overall output of the basal ganglia is predominantly via the thalamus, which then projects back to the PFC to form cortico-striatal-thalamo-cortical (CSTC) loops. Three CSTC loops are proposed to modulate executive function, action selection, and behavioral inhibition. In the dorsolateral prefrontal circuit, the basal ganglia primarily modulate the identification and selection of goals, including rewards.⁴⁴ The OFC circuit modulates decision-making and impulsivity, and the anterior cingulate circuit modulates the assessment of consequences.⁴⁴ These circuits are modulated by dopaminergic inputs from the VTA to ultimately guide behaviors relevant to addiction, including the persistence and

narrowing of the behavioral repertoire toward drug seeking, and continued drug use despite negative consequences.^{43–45}

The DS (also referred to as the caudate-putamen in primates) is associated with transitions from goal-directed to habitual drug use, due in part to its role in stimulus–response learning.^{28,46} As described above, the initial rewarding and reinforcing effects of drugs of abuse are mediated by increases in extracellular DA in the NAc shell, and after continued drug use in the NAc core.^{47,48} After prolonged drug use, drug-associated cues produce increases in extracellular DA levels in the DS and not in the NAc.⁴⁹ This lends to the notion that a shift in the relative engagement from the ventral to the dorsal striatum underlies the progression from initial, voluntary drug use to habitual and compulsive drug use.²⁸ In addition to DA, recent evidence indicates that glutamatergic transmission in the DS is important for drug-induced adaptations and plasticity within the DS.⁵⁰

Learning and memory systems

Hippocampus

The HPC is highly involved in normal spatial memory function, in part due to its critical involvement in the integration of contextual and environmental cues or information.⁵¹ Interestingly, the ventral subiculum, the primary output of the HPC, projects to several limbic regions, including the NAc and DS.⁵² The ventral subiculum has been found to play a key role in cocaine-seeking behavior, suggesting the importance of contextual information in psychostimulant addiction.⁵³ In addition, the ventral subiculum-to-NAc pathway has been implicated in psychostimulant sensitization in a DA-dependent manner.^{54,55} Recently, it was found that a trans-synaptic link between the CA3 region of the HPC and the VTA may also mediate the ability of contextual information to modulate motivational behaviors.⁵⁶ Microinjection studies by Fuchs and colleagues have also demonstrated a role for Glu transmission in the dorsal HPC in context-induced cocaine-seeking.⁵⁷

Amygdala

The AMG plays a prominent role in conditioned learning, wherein strong associations between environmental stimuli and the rewarding effects of drug use are made. Glutamatergic efferents from the AMG to the PFC, NAc, and HPC mediate behavioral responses to these stimuli.^{58–60} The AMG is composed of multiple nuclei that play distinct roles in addiction related associative learning. The stress neuropeptide CRF within the central nucleus of the AMG mediates various aspects of stress-motivated behaviors pertinent to addiction,

and drug-induced adaptations in CRF signaling have been found to occur within the AMG.^{61,62} In addition, the basolateral AMG is critical for cue-induced relapse, while the central nucleus of the AMG is a key neural substrate underlying stress-induced relapse.^{63–66} The reciprocal connections between the basolateral AMG and the anterior cingulate cortex may be particularly important for cocaine cue-induced relapse.^{67,68} Interestingly, the AMG and ventral subiculum themselves have reciprocal connections and have been found to project to the same population of NAc neurons.^{69,70} Thus, the outputs of the AMG and HPC interact and converge to modulate the reward circuitry and potentially solidify reward–context and reward–cue associations that contribute to the chronic relapsing characteristics of addiction.

Acute effects of psychostimulants

Mechanisms of action

As discussed above, a common neurobiological effect of many drugs of abuse is the direct or indirect modulation of DA-containing cell bodies in the VTA that target the NAc, resulting in the selective enhancement of extracellular DA levels in the NAc.^{20,72–74} However, not all drugs act directly on VTA dopaminergic neurons at the level of the cell bodies. Psychostimulants exert their effects through interactions with vesicular and plasma membrane monoamine reuptake transporters on presynaptic terminals in the NAc.⁷⁵ Cocaine binds transporters for DA, NE, and 5-HT and competitively inhibits their function, resulting in increased extracellular levels of DA, NE, and 5-HT in the NAc.⁷⁶ In transgenic mice lacking DA transporters (DATs), administration of cocaine did not result in enhanced locomotor activity or increased DA levels in the striatum, though these mice could learn to self-administer cocaine, potentially due to action at the NE and 5-HT transporters.^{77–79}

Amphetamines (AMPH and METH) exert their effects in a more complex manner. Rather than simply blocking DATs (or NE and 5-HT transporters) to increase extracellular monoamine levels in the NAc, amphetamines function to reverse the transport function of DAT, resulting in increased extracellular levels of DA. The exact mechanism of this reversal remains unclear.^{80,81} As part of this effect on DAT, amphetamines are transported into the presynaptic terminal via DATs and accumulate within the cytosol.⁸² An additional mechanism of action for amphetamines is to cause the redistribution of monoamines from synaptic vesicles to the cytosol.^{83,84} Several mechanisms for this redistribution have been suggested. Two primary hypotheses are that amphetamines act as a substrate at the vesicular monoamine

transporters (VMAT2 in neurons) or that they act as a weak base to collapse the vesicular pH gradient (see Rudnick and Clark⁷⁵ for review). Furthermore, amphetamines prolong monoaminergic transmission by inhibiting monoamine oxidase (MAO) activity and enhancing the activity of the rate-limiting DA synthetic enzyme tyrosine hydroxylase (TH).^{85–87} While NE and 5-HT levels also increase in the NAc as a result of stimulant use, increased extracellular DA plays a more prominent role in the initial rewarding and reinforcing properties of stimulants.⁷⁸ Interestingly, AMPH and METH are reported to be more potent releasers of NE than DA, and much less potent at releasing 5-HT.⁸⁹

Subjective effects and pharmacokinetics

Psychostimulants are associated with euphoria, increased self-confidence as well as increased energy, wakefulness and activity, with associated decreased fatigue and appetite.^{90–93} Adrenergic (sympathetic nervous system) effects of these drugs include elevated heart and respiration rate, blood pressure, body temperature, and sweating, in addition to increased tremor and exaggeration of reflexes.^{90,92,94,95} While different classes of illicit psychostimulants exert largely similar subjective effects, they differ in their pharmacokinetic properties. Cocaine has a short half-life of 30 minutes to 2 hours, and the time to peak subjective effects differs by route of administration.⁹⁶ When acidic cocaine (cocaine hydrochloride) is snorted, peak effects are felt within 10–15 minutes, while injection of acidic cocaine leads to peak effects within 3–4 minutes.^{97–99} Basic cocaine (“crack”) can be smoked and is considered more addictive, primarily due to the rapid peak effects (1–2 minutes).^{97,98} METH can also be administered via several routes, including oral, intravenous, and smoked.⁹⁹ As with cocaine, smoking METH leads to a more rapid “high,” potentially contributing to increased addiction liability of this route of administration.¹⁰⁰ METH has a much longer half-life (10–12 hours) compared to cocaine.¹⁰¹ AMPH is primarily used via oral or intravenous routes and also has a longer half-life of 10–14 hours.^{99,102} Various AMPH salt mixtures, such as D-AMPH, L-AMPH, are also used in medications to treat attention deficit/hyperactivity disorder, and are often described and alternatively categorized as prescription drugs. It is commonly thought that METH is more addictive than AMPH, which is supported by the finding that METH may have a stronger effect on DAT-mediated cell physiology and DA clearance in the NAc, though METH and AMPH do not differ in other pharmacokinetic properties or in the magnitude of DA release in the DS.^{103,104}

Chronic effects of psychostimulants

As previously described, drug addiction is considered a transitional process from casual drug use to habitual and uncontrolled drug use to dependence. Thus, different neurobiological adaptations likely underlie different stages of addiction. Several types of long-term changes can occur following prolonged drug use, including impairments in cognition and behavior, dysregulated functional connectivity within the brain, altered monoamine (primarily DA) receptor and transporter expression, and neurotransmitter synthesis and release. The focus of this section will be to provide a general picture of the long-term effects of chronic illicit psychostimulant use in humans. The majority of clinical research has focused on cocaine and METH users, with the frequent assumption that chronic AMPH use leads to similar outcomes as METH. Due to the variability in duration of drug abstinence in human subjects, the present review focuses on studies that utilized current psychostimulant users, or users in early stages of abstinence. For more detailed information on psychostimulant relapse, the reader is referred to several recently published reviews.^{105–107} In addition, a couple of caveats relevant to research on the chronic effects of psychostimulants in humans deserve to be mentioned. First, it is important to note that not every individual that experiences the acute effects of psychostimulants will become a chronic user. Individual predisposing factors, such as genetic vulnerabilities, trait impulsivity, socioeconomic status, early life experiences, and stress exposure, all significantly impact the addiction process. Secondly, only longitudinal studies in humans can truly determine whether the neuropsychological, psychiatric, or neuroanatomical differences in chronic psychostimulant users are a result of drug use or predisposing factors.

Neuropsychological effects

Chronic use of psychostimulants results in widespread impairments of neuropsychological functioning, including measures of memory, executive function, and mental flexibility. The primary brain regions mediating these cognitive impairments are the same as those implicated in the neurocircuitry of addiction, namely the PFC, AMG, HPC, and CSTC loops. Chronic cocaine users demonstrated impaired executive functions, including measures of attention, working memory, set-shifting, mental flexibility, and response inhibition.¹⁰⁸ In one measure of PFC-mediated executive function, the Wisconsin Card Sorting Task, both METH-dependent subjects and chronic cocaine users demonstrated significant impairments (ie, increased perseverative responding).^{109–111} In addition,

cocaine-dependent subjects exhibit poor performance on a delayed-discounting and reversal-learning task.¹¹² In another study, chronic cocaine users, but not AMPH users, demonstrated increased perseverative responding in a probabilistic reversal-learning task.¹¹³

METH-dependent subjects also exhibit impaired global neuropsychological function, specifically in the domains of executive function, learning, motor ability, and speed of information processing.¹¹⁴ These impairments improved significantly following a period of abstinence.¹¹⁴ The same study found no effects of chronic METH use on measures of memory, working memory, or verbal abilities.¹¹⁴ However, other studies found that METH-dependent subjects exhibited impaired visual memory and executive control of verbal learning.^{115,116} Differences between these studies on the effects of METH on verbal processes and memory may be in part due to differing histories of METH use in METH-dependent subjects across studies.^{2,3} METH-dependent subjects were also impaired in measures of real-life skills, such as comprehension, finance, transportation, communication, and medication management.¹⁰⁹ In addition, METH abusers demonstrated impaired social cognition, as measured by facial emotion-recognition tasks, especially with respect to fear recognition.¹¹¹ Interestingly, impairments in executive function and social cognition have been found to be positively correlated.^{4,111,117} In another study, METH-dependent subjects demonstrated slower reaction times and increased error and response-inhibition rates on a “go/no go” task.¹¹⁸ These performance deficits were more severe in the presence of cue-elicited craving.¹¹⁸

Neurological and psychiatric effects

Psychosis is a common effect of chronic psychostimulant abuse. Psychotic symptoms include both hallucinations and delusions. Lifetime use of cocaine, but not AMPH, is associated with the experience of psychotic symptoms after adjusting for demographic covariates, comorbidity, and childhood adversity.¹¹⁹ Severity of psychosis as a result of long-term psychostimulant abuse is increased in those that begin using at younger ages and use for longer periods of time.¹²⁰ Interestingly, cocaine- and METH-dependent women are more likely than men to experience a variety of psychotic symptoms, including delusions of grandeur and tactile hallucinations.¹²¹ Chronic use of psychostimulants is also associated with various other psychiatric disorders, including mood and anxiety disorders. METH users are more likely than cocaine users to have a comorbid psychiatric diagnosis, such as major depression, bipolar disorder, and anxiety disorders.¹²² A separate study found that METH-dependent

subjects reported increased depressive symptoms and acute affective distress compared to control subjects, and that these symptoms improved following a period of abstinence.¹¹⁴

A more unusual effect of chronic psychostimulant use is formication, the sensation of organisms crawling under one's skin, which has been reported by both chronic METH and cocaine users.⁹⁴ These "meth mites" or "crank bugs" frequently lead to excessive skin picking, sores, and infections.^{123,124} Other neurological effects of chronic psychostimulant use include punding (engagement in purposeless and repetitive activities, such as assembling and disassembling electronics), grooming behaviors, and dyskinesias.¹²⁵⁻¹²⁷ With regard to the latter, choreoathetoid movements (involuntary and aimless movements; also known as "crack dancing") are associated with both AMPH and cocaine abuse.¹²⁸ Interestingly, many of the neurological and psychiatric effects of chronic psychostimulant use, with the exception of altered mood and psychosis, are symptoms related to altered functioning in the striatal region of the basal ganglia and are likely a result of damage to dopaminergic terminals.

Neurocircuitry: brain imaging

Functional effects

Chronic psychostimulant use is associated with alterations in functional connectivity, white- and gray-matter densities, and activation of distinct brain regions underlying reward and cognitive function. Connectivity and activation studies are conducted with various iterations of magnetic resonance imaging (MRI), while density studies utilize either MRI or diffusion tensor imaging. A greater number of studies have been conducted in cocaine-dependent individuals than AMPH or METH users. In a detailed study using resting-state functional MRI connectivity analysis with seed voxels, cocaine users exhibited decreased connectivity between (1) the VTA and the region encompassing the thalamus/lentiform nucleus/NAc, (2) the AMG and mPFC, and (3) between the HPC and dorsal mPFC.¹²⁹ These changes in the neurocircuitry of the cocaine-addicted brain are consistent with maladaptive or impaired reward processing, learning, memory, and emotional regulation.¹²⁹ Interestingly, connectivity between the NAc and cortical regions was not reduced, potentially lending credence to the role of habitual drug use in addiction, which is more tightly regulated by the DS.¹²⁹ Several studies suggest that cocaine addiction results in altered engagement of frontoparietal networks during attentional tasks.^{130,131} Recently it was found that cocaine abusers exhibited reduced functional connectivity between the midbrain, where DA neurons are situated, and cortical

and subcortical brain regions during an attentional Stroop task that tested the processing of drug and neutral words.¹³² Reduced activation in the right parietal cortex, a region involved in attention, during the two-back verbal working memory task was also found in cocaine-dependent males.¹³³ In a study investigating the neural underpinnings of drug craving, chronic cocaine use was associated with enhanced reactivity to drug-associated cues, paralleled by enhanced connectivity between the left dorsolateral PFC and occipital cortex compared to healthy control subjects.¹³⁴ In addition, the OFC was activated significantly more in cocaine users in response to cocaine cues, but not appetitive stimuli.¹³⁴ It has also been found that chronic cocaine users demonstrate impaired sensorimotor abilities that are accompanied by abnormal activity in the cortical and subcortical brain areas involved in motor control.¹³⁵

Structural effects

Cocaine users have reduced subcortical gray-matter density which negatively correlates with impaired performance in psychomotor performance, recognition and working memory, and planning.¹³⁶ Interestingly, in a study that included cocaine- and AMPH-dependent subjects, reduced gray-matter volume in the medial OFC was found, which correlated with increased high-risk decisions in a modified gambling task.¹³⁷ Likewise, cocaine-dependent subjects demonstrated impaired decision-making on the Iowa gambling task, which correlated with compromised frontal, parietal, and corpus callosum white-matter integrity.¹³⁸ In addition, abnormalities in white-matter microstructure underlying the PFC and HPC are associated with chronic METH use, during both late and early abstinence.^{139,140} Chronic METH use is also associated with gray-matter deficits in the cingulate and limbic cortices, reduced hippocampal volume, and white-matter hypertrophy in the temporal regions around the HPC.¹⁴¹ These cortical and hippocampal abnormalities likely contribute to impaired memory performance found in chronic METH users, while white-matter hypertrophy may be related to altered glial changes.¹⁴¹ Additionally, decreased temporal lobe, but not frontal lobe, volume was found in both AMPH- and cocaine-dependent subjects.¹⁴²

Effects on molecular substrates: DA receptors, DAT, and VMAT

Postmortem studies

Repeated psychostimulant use can alter DA receptor and transporter expression in several brain regions. Most human postmortem studies have focused on DAT expression in

cocaine-dependent subjects. The majority of these studies, which used either saturation-binding or autoradiography techniques, demonstrated increased DAT binding in the striatum of cocaine-dependent subjects compared to control subjects (see Table 1 in Rajesh and Diana).¹⁴³ However, others have found decreased DAT-binding sites in the postmortem PFC from chronic cocaine users compared to non-cocaine-using controls.¹⁴⁴ In the postmortem striatum of METH users, decreased TH immunoreactivity and DAT levels were found.¹⁴⁵ In a subset of individuals, VMAT2 levels were also significantly reduced, though this were not common.¹⁴⁵ Another postmortem study in chronic METH users found decreased levels of DA, TH, and DAT in the striatum, but normal levels of L-3,4-dihydroxyphenylalanine (DOPA) decarboxylase (the enzyme that converts L-DOPA into DA) and VMAT2.¹⁴⁶ The authors concluded that chronic METH use does not cause permanent degeneration of striatal DA nerve terminals. Postmortem studies of VMAT2 expression in the striatum of cocaine abusers have had mixed results, with two

studies finding decreased VMAT2 and one study finding no change.^{147–149}

Imaging studies

Imaging studies of receptor and transporter expression are typically conducted with positron-emission tomography (PET). Imaging studies, while sacrificing spatial resolution, avoid some of the limitations of postmortem studies, such as antemortem tissue events, varied time since death, and undocumented life-history events. The majority of these types of studies have again focused on the availability of DA receptors and transporters and VMAT2, as well as DA uptake and synthesis. In chronic cocaine abusers, VMAT2 availability was decreased in the NAc (referred to as the ventral striatum) and DS (referred to as the associative and sensorimotor striatum) compared to control subjects.¹⁵⁰ This may reflect potential compensatory downregulation in response to loss of DA terminals.¹⁵⁰ Stimulant-induced DA release, as measured by displacement

Table 1 Summary of acute and chronic effects of psychostimulants in humans

Acute effects	Cocaine	METH/AMPH
Primary site of action	Presynaptic monoaminergic terminals in NAc.	Presynaptic monoaminergic terminals in NAc.
Mechanism of action	Inhibition of DA, NE and 5-HT transporters.	Reverse DA, NE, 5-HT transporter function. Redistribution monoamines to cytosol via VMAT2.
Half-life	30 minutes–2 hours.	10–14 hours.
Subjective effects	Euphoria, increased libido and self-confidence. Increased energy, wakefulness and activity. Decreased appetite and fatigue.	
Adrenergic effects	Elevated heart rate, blood pressure and rapid breathing. Elevated body temperature and sweating. Tremor and exaggeration of reflexes.	
Chronic effects		
Neuropsychological	Impaired executive function, learning, mental flexibility. Impaired motor abilities and reaction time. Impaired information processing and social cognition.	
Psychiatric and Neurological	Psychosis, comorbid psychiatric disorders such as depression and anxiety. Formication (skin picking at “METH mites” or “crank bugs”), punding (purposeless and stereotyped behavior) and choreoathetoid (twisting and aimless) movements.	
Neurocircuitry	Decreased functional connectivity and activation within the reward circuitry and cortical and subcortical regions mediating executive function, learning and memory. Reduced subcortical gray matter. Reduced integrity and abnormalities in white matter in the HPC, PFC and other cortical regions.	
Molecular substrates Post-mortem	Majority find increased striatal DAT. No consensus on striatal VMAT2.	Decreased striatal DA, DAT and TH levels. Normal striatal VMAT2 levels. Increased number of microglia in the striatum.
Molecular substrates Imaging	Decreased striatal VMAT2 availability. Blunting of striatal DA system function. Decreased striatal D2 receptor availability.	Increased striatal VMAT2, abstinence-dependent. Decreased DAT in the striatum, PFC, and AMG.

Note: See text for citations, more detailed descriptions, and discrepancies.

Abbreviations: AMG, amygdala; AMPH, D-amphetamine; DA, dopamine; DAT, dopamine transporter; HPC, hippocampus; METH, methamphetamine; NAc, nucleus accumbens; NE, norepinephrine; PFC, prefrontal cortex; VMAT2, vesicular monoamine transporter 2; 5-HT, 5-hydroxytryptamine (serotonin).

of DA receptor-antagonist radiotracers, was decreased in the striatum of cocaine-dependent subjects with 2–6 weeks of abstinence, indicating a blunting of striatal DA system function as a result of chronic cocaine use.^{151,152} PET studies have also found a significant decrease in striatal DA synthesis, as measured by [¹⁸F]6-FDOPA uptake, in cocaine-dependent subjects. However, this was only evident in subjects that had been abstinent for greater than 10 days.¹⁵³ Decreased striatal D₂ receptor availability was also found in both cocaine- and METH-dependent subjects.^{152,154–156}

In METH users, striatal VMAT2 binding was significantly increased with decreasing duration of abstinence (ie, 3 vs 21 days).¹⁵⁷ These findings are in opposition to the slight increase in striatal VMAT2 binding found in METH abusers after long-term abstinence (ie, years).¹⁵⁸ The disparity between these findings suggests that the time since last drug use is a critical variable that must be accounted for and controlled for in human studies. Most studies in METH-dependent subjects use currently abstinent subjects, but in those that were abstinent for an average of 6 months, decreased DAT was found in the DS (referred to as the caudate and putamen), NAc, PFC, OFC, and AMG.^{159–161} Unlike with VMAT2, increased duration of abstinence was associated with increased striatal DAT density.¹⁶²

Note on inflammatory effects

Repeated use of high doses of METH results in neurotoxicity in preclinical models, particularly in the striatum (for review, see Krasnova and Cadet).¹⁶³ While the mechanism underlying METH-induced neurotoxicity has not been fully elucidated, it is likely due to repeated, high levels of extracellular DA leading to production of quinones and free radicals such as reactive oxygen species.^{164,165} Studies in humans have investigated the role of inflammatory mediators in METH-induced neurotoxicity, due to the fact that microglial activation has been associated with METH neurotoxicity in animal models.¹⁶⁶ Interestingly, the number of microglia but not activation of glial cells in the postmortem striatum of METH users was significantly increased.¹⁴⁵ A follow-up study confirmed and extended these results in non-abstinent METH users, finding that METH use results in significantly increased striatal microglia in the absence of reactive gliosis.¹⁶⁷ However, in abstinent METH abusers, a PET study found a significant increase in binding of a radiotracer (PK11195) for activated microglia in all brain regions.¹⁶⁸ In adults in remission from METH dependence, immune-system dysregulation was found, in addition to significant cognitive impairments, which encompassed learning,

memory, and attentional/informational processing.¹⁶⁹ In the same study, impaired global cognition was significantly and positively correlated with plasma levels of the cytokine alpha-interferon.¹⁶⁹ In addition, a decrease in the anti-inflammatory marker interleukin 10 and increased proinflammatory tumor necrosis factor alpha in response to stress exposure has been found in cocaine abusers (compared to social drinkers), potentially indicating an elevated inflammatory state.¹⁷⁰ Interestingly, postmortem brain studies suggest that cocaine addiction is not associated with increased activation of markers of apoptotic cell-death pathways.^{47,171} Together, these initial studies indicate dysregulated inflammatory processes following chronic psychostimulant use in humans and provide evidence to support the need for further investigations.

Implications for the treatment of substance abuse

At present, no pharmacological therapy has been approved by the FDA to treat psychostimulant addiction. Many drugs have been tested, but none have shown conclusive efficacy with tolerable side effects in humans.¹⁷² These drugs have included DA-receptor ligands, such as DA receptor agonists, partial agonists, and antagonists, as well as DA-reuptake inhibitors.^{173,174} One newer dopaminergic drug that has shown some promise is the antipsychotic medication aripiprazole, a partial agonist at D₂-like receptors, which is currently approved for the treatment of schizophrenia, depression, and bipolar disorder.¹⁷⁵ Clinical trials have thus far been mixed, with one study finding reduced cocaine craving and use, and another study showing increased cocaine use.^{176,177}

Recent evidence for dysregulation of glutamatergic signaling in addiction has led to the testing of *N*-acetylcysteine, a derivative of the amino acid cysteine that normalizes extracellular levels of Glu following cocaine administration.^{178,179} Clinical trials found that *N*-acetylcysteine treatment attenuates cocaine craving and use and normalizes brain glutamate levels.^{180–182} Other recent studies found trends toward significant reductions in METH use and craving produced by the antidepressant bupropion and the anticonvulsant topiramate, which has glutamate release-inhibiting properties.^{183,184} While these compounds have not demonstrated overwhelming efficacy in reducing psychostimulant use or craving in all subjects tested, trends toward effects were observed and thus merit further investigation.

Other compounds that have been tested, with disappointing results, include β -adrenergic antagonists,

opioid-receptor antagonists, 5-HT₃-receptor antagonists, antidepressants, and anticonvulsants.^{172,185–190} Despite the lack of past successes, several newer medications are currently being investigated and have shown some initial success, such as the smoking-cessation aid varenicline, the α_2 adrenergic agonist clonidine, and the antidepressant mirtazapine.^{191–194} In addition, preclinical evidence strongly suggests potential therapeutic effects of compounds targeting receptors for endocannabinoids, the neuropeptide orexin, and CRF for the prevention of relapse to psychostimulant use.^{195–197}

Future approaches for the treatment of psychostimulant-induced cognitive deficits and dependence include the use of cognitive enhancers.^{198–200} Two promising examples include prescription stimulants, such as modafinil and methylphenidate, which have shown modest but potential treatment effects in METH users and cocaine users with comorbid attention deficit/hyperactivity disorder, respectively.^{201–205} In addition, galantamine, a cholinergic modulator and cognitive enhancer, has been reported to both decrease cocaine use and improve sustained attention in dependent subjects.^{206,207} Together, these studies indicate that clinical trials of cognitive enhancers in the treatment of psychostimulant addiction are warranted.

In addition to the pharmacological trials reviewed above, less conventional strategies that are gaining scientific momentum include vaccine therapies to immunoneutralize drug molecules and impede penetrance across the blood–brain barrier, enzyme conjugates that dramatically increase the metabolic breakdown of abused drugs, pharmacogenetic approaches based on individual genetic polymorphisms in addiction-related genes, and epigenetic modulators of drug-induced changes in gene expression.^{208–211} While still in their relative infancy, these exciting new avenues of research offer a significant expansion of possible biologically based targets for the treatment of psychostimulant addiction.

Conclusion

Even with over half a century of research directed at understanding the mechanisms and treatment of psychostimulant addiction, this disorder remains a serious socioeconomic problem. Psychostimulants exert their acute rewarding and reinforcing actions primarily via direct and indirect release of extracellular DA in the NAc. DA release in other brain regions, such as the PFC and AMG, play a role in behavioral control and learned associations between environmental stimuli and the subjective rewarding effects. In addition to DA release, psychostimulants also

alter other neurotransmitter systems, such as 5-HT, NE, Glu, endocannabinoids, and various neuropeptides. With continued drug use, other regions, such as the DS and CSTC, may mediate such behaviors as action control and habitual or compulsive drug seeking. Chronic drug use leads to persistent adaptive changes within the reward circuitry, including altered receptor and transporter expression, neurotransmitter release, and functional connectivity between brain regions. Ultimately, these adaptive changes are associated with an impaired cognitive state and neuropsychiatric symptoms. While some of the effects of chronic psychostimulant use may dissipate with increasing abstinence, many chronic users are unable to achieve or maintain even a short period of abstinence.

The tremendous need for more effective pharmacological treatments for psychostimulant addiction is a mainstay of contemporary addiction research. However, the recent downsizing of many major pharmaceutical companies away from psychiatric indications (including addiction) due to the lack of efficacy of experimental compounds in humans may require a sea change in the translational research approach.^{212,213} A new emphasis on larger-scale biomarker, genetic, and epigenetic research focused on the molecular targets of mental disorders has been recently advocated.²¹² In addition, the integration of cognitive and behavioral modification of circuit-wide neuroplasticity (ie, computer-based training to enhance executive function) may prove to be an effective adjunct-treatment approach for addiction, particularly when combined with cognitive enhancers.^{198,213–216} Furthermore, in order to be effective, all pharmacological or biologically based treatments for addiction need to be integrated into other established forms of addiction rehabilitation, such as cognitive behavioral therapy, individual and group psychotherapy, behavior-modification strategies, twelve-step programs, and residential treatment facilities.

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Disclosure

The authors report no conflicts of interest in this work.

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