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**Keywords**

dopamine, addiction, addictive drugs

**Abstract**

Addiction is commonly identified with habitual nonmedical self-administration of drugs. It is usually defined by characteristics of intoxication or by characteristics of withdrawal symptoms. Such addictions can also be defined in terms of the brain mechanisms they activate; most addictive drugs cause elevations in extracellular levels of the neurotransmitter dopamine. Animals unable to synthesize or use dopamine lack the conditioned reflexes discussed by Pavlov or the appetitive behavior discussed by Craig; they have only unconditioned consummatory reflexes. Burst discharges (phasic firing) of dopamine-containing neurons are necessary to establish long-term memories associating predictive stimuli with rewards and punishers. Independent discharges of dopamine neurons (tonic or pacemaker firing) determine the motivation to respond to such cues. As a result of habitual intake of addictive drugs, dopamine receptors expressed in the brain are decreased, thereby reducing interest in activities not already stamped in by habitual rewards.

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## Contents

INTRODUCTION .....	80
THE DOPAMINE SYSTEM AND BEHAVIOR .....	81
Dopamine-Depleted Animals Have Only Unconditioned Reflexes .....	81
Phasic Dopamine Responses: Burst Firing and Instrumental Learning .....	82
Low Dopamine Levels Are Aversive .....	85
Tonic Dopamine Release Determines Motivational Arousal .....	86
Dopamine Receptors Are Downregulated by Habitual Reward Seeking .....	87
ADDICTIVE DRUGS .....	88
Addictive Drugs Are Habit-Forming and Activate the Dopamine System .....	88
Cocaine .....	88
Amphetamines .....	90
Opiates .....	90
Alcohol .....	91
Nicotine .....	91
Marijuana .....	92
Barbiturates and Benzodiazepines .....	92
Caffeine .....	93
Other Forms of Addiction .....	93

## INTRODUCTION

Addiction refers to the compulsive nonmedical self-administration of drugs. Often used pejoratively, the term refers to drug taking done by other people or to drug taking despite negative side effects. The latter notion has been inferred from a statement by Alan Leshner (1997, p. 46), head of the National Institute on Drug Abuse, describing addiction as “compulsive drug seeking and use even in the face of negative health and social consequences.” Negative consequences have been added to the discussion of addiction, as modeled by animals pressing a lever for a cocaine reward accompanied by either footshock (Deroche-Gamonet et al. 2004) or a tone previously associated with footshock (Vanderschuren & Everitt 2004). However, the idea of negative consequences is a human issue, and for humans, negative consequences are rarely experienced at the time of drug taking. Rather, they are the imagined future consequences, read about or heard about, such as possible or probable cancer, heart problems, or incarceration. This notion of addiction has narrowed the discussion to drug addiction and links the phenomenon to drugs like heroin and alcohol that, when withdrawn, have prominent aversive withdrawal symptoms.

One problem with these definitions is that they do not apply equally across the range of addictive drugs and they do not apply equally to other powerful rewards. Thus, arguments develop around issues such as whether marijuana, gambling, or high-calorie food is addictive.

Although the direct effects and withdrawal symptoms vary across addictive drugs, all such drugs and some other rewards impact the brain reward system and the extracellular fluctuations of the implicated neurotransmitter dopamine. In this review, we first discuss the role of dopamine in physiology and behavior and then describe how addictive drugs and substances activate the dopamine system to perpetuate maladaptive behavior.

## THE DOPAMINE SYSTEM AND BEHAVIOR

Dopamine is a neurotransmitter: a chemical synthesized by neurons and released in ways that influence the activity of other neurons. It is sometimes identified as a neuromodulator—a subtype of neurotransmitter—because it acts more to modulate the sensitivity to other neurotransmitters rather than substituting for them. In the striatum, where it has its most obvious, but not only, motivational functions, dopamine modulates the excitatory control of glutamate-releasing input neurons on GABA-releasing output neurons. Dopamine facilitates the development of long-lasting cellular modifications that either potentiate or depress the influence of glutamate, and these adaptations determine the effectiveness of reward predictors to control subsequent search behaviors. Discussed in the following sections, four aspects of dopamine function are related to addiction: (a) Animals lacking dopamine have only unconditioned reflexes, (b) phasic firing of dopamine neurons stamps in (reinforces) learning, (c) tonic firing of dopamine neurons controls or contributes to motivation, and (d) habit reliance decreases interest in other incentives.

### Dopamine-Depleted Animals Have Only Unconditioned Reflexes

Adult animals with selective damage to their dopamine system are akinetic. If not artificially fed, they die of starvation (Anand & Brobeck 1951, Stricker & Zigmond 1976, Ungerstedt 1971). They have adequate motor capacity: They respond to footshock (Cooper et al. 1973, Laverty & Taylor 1970); retain the ability to shake their heads, groom, and attempt to escape from restraint; if placed in deep water, they swim; and if placed in an ice bath, they escape (Keefe et al. 1989). However, dopamine-depleted animals do not show spontaneous movements in an open field (Ungerstedt 1971); are only minimally responsive to mild touch, auditory, or visual stimuli; and fail to follow moving stimuli or respond to food odors (Marshall & Teitelbaum 1974, Marshall et al. 1971). These animals reject water or food offered in standard tests, allowing it to dribble onto the floors of their cages (Anand & Brobeck 1951, Stricker & Zigmond 1976, Ungerstedt 1971). Simply put, these animals have unconditioned reflexes and habits learned prior to being lesioned, but they cannot learn new responses. Moreover, after being lesioned, they lack motivation to react to predictive stimuli. This is critical for life; predictive stimuli guide the animal from one reward to another (Bindra 1969, Bolles 1972).

Cell biologists can alter the ability of animals to synthesize tyrosine hydroxylase—a dopamine precursor—from nutrients. Such animals die in utero because of heart failure. However, if the ability to synthesize the by-products of dopamine—two related neurotransmitters norepinephrine and epinephrine—is restored, then the animals are born normally and survive for a few weeks. They lose weight, are hypoactive, groom only minimally, and have hunched posture (Zhou & Palmiter 1995). Like normal animals depleted of dopamine, they fail to search for and bite at food; if not treated, they also die of starvation (Palmiter 2008). In this case, the animals never learned to respond to predictive stimuli; they also have only unconditioned (Pavlov 1927) consummatory (Craig 1918) reflexes.

The impairments in tyrosine-deficient mice can be reversed by infusions of the dopamine-precursor L-DOPA (Denenberg et al. 2004, Heusner et al. 2003, Zhou & Palmiter 1995). This precursor is taken up and metabolized to dopamine, which is stored by the traditional neurons and becomes released when these neurons are active. Twice-daily L-DOPA injections are sufficient to maintain nearly normal body weight in these animals (Zhou & Palmiter 1995); once-daily L-DOPA injections restore feeding for approximately 8 hours, but this is not sufficient for survival (Szczypka et al. 1999). Injections of direct dopamine agonists—drugs that act at dopamine receptors—independent of whether the dopamine system is active—are not effective; indeed, they have the opposite effect. It is necessary to have dopamine released only at times when the cells are

activated (Sotak et al. 2005). Local delivery of genes for synthesis of tyrosine hydroxylase (and of a required cofactor) can restore dopamine function in localized regions. Dorsal striatal injections restore the ability to eat and drink (Szczypka et al. 2001), search for pups (Henschen et al. 2013) and perform maternal behavior (Henschen et al. 2013), whereas ventral striatal injections restore normal locomotion, a component of finding distant rewards (Heusner et al. 2003).

In summary, dopamine depletion leaves animals unable to learn conditioned reflexes. Animals born without dopamine never develop conditioned reflexes, and animals that lose their dopamine systems as adults have the memory traces for conditioned reflexes but no longer show these responses to predictive stimuli. The ability of the system to condition burst responding to reward predictors allows an animal to learn to find food, shelter, and social contacts and help it to avoid painful or threatening stimuli.

### **Phasic Dopamine Responses: Burst Firing and Instrumental Learning**

Search habits depend on the learning of associations between unconditioned rewarding stimuli and the stimuli that immediately preceded (predicted) them. In addition, two sources of neuronal plasticity are involved: One occurs between excitatory terminals and the dopamine neurons (Saal et al. 2003), and the other occurs between the striatal glutamatergic excitatory inputs and GABAergic output neurons that receive modulating synaptic input from the dopamine system. Although studies of dopamine projections to the striatum have dominated the literature, the dopamine system projects to other parts of the brain, and lesion and pharmacological studies suggest that they play similar, but not identical, roles in drug seeking and drug withdrawal (McGregor et al. 1994, 1996).

#### **The dopaminergic response to rewarding stimuli is phasic activation (burst firing).**

Dopamine neurons have an unconditioned response to intense stimuli (Horvitz 2000), novel stimuli (Ljungberg et al. 1992, Steinfels et al. 1983), rewards, and punishers (Chiodo et al. 1979, Schultz 1986, Strecker & Jacobs 1985); its response is termed phasic activation, better known as burst firing. The responses to punishers are complex, but the responses to rewards such as food are reflexive, linked, bursts of discharges (Schultz 1986). Similar responses develop in response to predictors of food as a result of contiguity; through repeated associations between predictors and food, dopamine neurons come to respond with bursts to stimuli that immediately precede and reliably predict the reward (Ljungberg et al. 1992). As immediate predictors are learned, burst responses develop to increasingly earlier predictors (Schultz et al. 1993). As discussed below, predictors of addictive drugs also develop burst responses in the dopamine system.

Burst firing involves groups of two to approximately eight discharges (occasionally longer) in response to excitatory inputs (Grace & Bunney 1984b). Bursts can be separated from spontaneous firing by the intervals and intensities of successive action potentials; there are decreasing amplitudes of successive discharges, and the intervals between the first and second potentials (~60 ms) and between subsequent intervals (~120 ms) are short (Grace & Bunney 1984b). In contrast, single-spike discharges are longer and more variable, with mean intervals between 150 and 500 ms (Grace & Bunney 1984b). Burst firing is triggered by glutamatergic or cholinergic inputs to the dopamine system (Grace & Bunney 1984a); these inputs arise from two related sensory nuclei in the brainstem, the laterodorsal and pontine tegmental nuclei (Floresco et al. 2003, Lodge & Grace 2006).

The responses to punishing stimuli are also important in studies of addiction, but they remain to be fully understood. Not all dopaminergic neurons burst in response to punishers; some dopamine neurons are inhibited by punishers and punishment-predictors (McCutcheon et al.

2012). Further research is needed in this area because recent evidence suggests that, in rats, predictors that cocaine will be delayed, not available at the time an animal is ready to work for it, become aversive. Aversive stimuli establish an aversive state of mind, a state the addicted animal avoids by taking more cocaine (Wheeler et al. 2015). It seems likely that a similar pattern of acquired motivation will be found for other addictive drugs.

**Phasic release of dopamine is detected by fast-scan cyclic voltammetry.** There has been long-standing debate about the methods used to measure extracellular dopamine. Microdialysis detects concentrations of dopamine well below 1.0 nM (Westerink et al. 1987a) but may underestimate dopamine levels by chronically depleting the local analyte and by disturbing and altering the tissue around the large dialysis probe (Benveniste 1989, Nesbitt et al. 2013). Voltammetry has a detection threshold of approximately 20 nM (Owesson-White et al. 2012), too high to measure baseline firing (as suggested by no-net-flux microdialysis; see below) (Parsons & Justice 1992, Sam & Justice 1996). Thus, voltammetry detects some, but does not provide an indication of all, phasic discharges from the local dopamine terminals.

Voltammetry has been progressively refined over the past two decades, such that one version—fast-scan cyclic voltammetry (FSCV)—identifies only bursting release of dopamine accumulations, reaching well above 20-nM concentrations (Fox & Wightman 2017, Owesson-White et al. 2012). Burst firing saturates the dopamine uptake mechanism and causes accumulations of dopamine that penetrate into this range (Gonon 1988). However, the concentrations from bursts are localized. Concentration decreases rapidly from the site of dopamine release, diffusing to baseline levels as it spreads a few micrometers from the release site (Cragg & Rice 2004, Rice & Cragg 2008). The FSCV method uses small probes that allow them—after required adjustments of probe placement (Phillips et al. 2003, Robinson et al. 2001)—to be near enough to release sites for such detection. A subsecond sampling method is used (10-ms samples every 100 ms) (Robinson et al. 2001), enabling FSCV to detect the accumulating local levels from repeated firing in bursts (Gonon 1988). Finally, background subtraction—the removal of the momentary value measured immediately prior to the observed peaks—eliminates the contribution of the baseline dopamine signal (Heien et al. 2004). By background-subtracting baseline dopamine levels, current FSCV eliminates any indication of the baseline dopamine levels contributed by single impulses.

Thus, the most reasonable interpretation is that FSCV identifies the fast, local, and cue-induced fluctuations of variably placed synapses in the striatum, whereas microdialysis measures primarily the slow, distributed, and temporally averaged changes due to fluctuations associated with the motivational state of the animal (discussed in the section titled Tonic Activation Is Measured by Microdialysis). FSCV removes from its estimates any contributions of tonic firing, reflecting only a portion of accumulated concentrations due to local phasic firing and detecting burst release that is important for stamping in temporally and spatially distributed memory traces. Microdialysis is relatively insensitive to phasic firing because it averages firing that is spatially and temporally distributed, such that individual and peak concentrations are largely lost by uptake and diffusion into background concentrations.

**The dopamine system is heterogeneous.** Both the dopamine system and the synaptic targets of the dopamine system are heterogeneous. The dopamine system projects to the striatum, medial prefrontal cortex, hippocampus, amygdala, and other areas (Menegas et al. 2018, Ogawa & Watabe-Uchida 2017), each of which serves different functions. Some dopamine neurons respond to unconditioned rewards (Ljungberg et al. 1992); others respond to unconditioned punishment (Brischoux et al. 2009, Lammel et al. 2011). Some respond to otherwise neutral stimuli that have come to predict reward (Ljungberg et al. 1992); others respond to otherwise neutral stimuli that

have come to predict punishment (Mileykovskiy & Morales 2011). Even within the reward category, a predictor of feeding may modulate moving to where the food will appear while another modulates approaching a possible social partner. Thus, there is heterogeneity in the responses of dopaminergic neurons themselves.

Within the striatum, close to half of the output neurons express only D<sub>1</sub> receptors, and the other half express only D<sub>2</sub> receptors (only a few cells express both) (Gerfen & Surmeier 2011). D<sub>1</sub> receptors have low affinity for dopamine (Rice & Cragg 2008, Richfield et al. 1989) and are thus infrequently occupied by dopamine molecules. When D<sub>1</sub>-expressing output neurons are activated, they encourage action (Kravitz et al. 2012). D<sub>2</sub> receptors have high affinity for dopamine (Rice & Cragg 2008, Richfield et al. 1989) and are usually occupied by dopamine molecules (Dreyer et al. 2010). When D<sub>2</sub>-expressing medium spiny neurons are further activated, they are generally thought to inhibit action (Kravitz et al. 2012). D<sub>1</sub>- and D<sub>2</sub>-expressing output neurons have distinct projection targets, although there is some overlap from the ventral striatal output neurons (Kupchik et al. 2015). The distinction between D<sub>1</sub> and D<sub>2</sub> activations was once thought to mediate periods of activity and alternating periods of inactivity, but we now know that in the dorsal striatum D<sub>1</sub> and D<sub>2</sub> striatal neurons are usually activated at or nearly at the same times (Cui et al. 2013, Tecuapetla et al. 2016). Therefore, dopamine's activation of D<sub>1</sub> striatal neurons appears to enable one set of movements while its activation of D<sub>2</sub> striatal neurons disables multiple sets of potentially conflicting movements.

**Phasic activation of dopaminergic neurons modifies synaptic transmission.** Phasic activation of the dopamine system by unconditioned rewards is essential for establishing the link between potentially predictive environmental stimuli and the unconditioned rewards that follow them (Ljungberg et al. 1992, Schultz 1997); these connections result from synaptic changes in the brain. In the striatum, medium spiny neurons show long-term potentiation (an increase in sensitivity to presynaptic input) or long-term depression (a reduction in sensitivity to presynaptic input) of synaptic transmission, and dopamine receptor activation is critically involved in these synaptic modifications (Creed et al. 2016, Gerfen & Surmeier 2011). Electrical self-stimulation of the dopamine system, causing burst firing, results in long-term potentiation of forebrain synapses, and this plasticity involves D<sub>1</sub> receptor activation (Reynolds et al. 2001, Wickens et al. 2003); the medium spiny neuron must receive glutamatergic and dopaminergic input within the same 0.3–2.0-s time window for the potentiation of the glutamate connection to GABAergic output neurons (Yagishita et al. 2014). These plastic changes are important for learning a stimulus chain to find rewards, and they can be driven by the rewarding effects of drugs of abuse (Creed et al. 2016, Zhu et al. 2016). The same input promotes long-term depression of excitatory signaling in D<sub>2</sub>-expressing striatal neurons, which is important for suppressing competing response options to those driven by potentiated inputs to D<sub>1</sub>-expressing striatal neurons.

Learning of this type is distributed across structures; dopamine enhancement in the dorsal striatum is involved in learning to repeat responses that have just been rewarded, but other structures learn other associations (McDonald & White 1993). However, even within the striatum, there is further differentiation of function, as adjacent neurons can participate in distinct tasks (Carelli & Deadwyler 1994, Roop et al. 2002). In the striatum, coincident activation of dopamine D<sub>1</sub> receptors and NMDA (*N*-methyl-*D*-aspartate) receptors is required for long-term facilitation (Beutler et al. 2011, Smith-Roe & Kelley 2000). Dopamine neurons also undergo long-term potentiation (Saal et al. 2003); however, in this case, NMDA receptors are not involved (Parker et al. 2010).

Recent optogenetic studies have confirmed a causal link between phasic activation of the dopamine system and reward learning. Animals learn to lever press resulting in optogenetic

activation of dopamine neurons, which is sufficient to condition nose-poking or lever-pressing habits (Ilango et al. 2014, Witten et al. 2011). Animals will also respond to optogenetic stimulation limited to dopaminergic terminals in the nucleus accumbens, depending on both D<sub>1</sub> and D<sub>2</sub> receptor activation (Steinberg et al. 2014). As predictors of reward become associated with rewards, they elicit burst firing of dopamine neurons; the resultant phasic dopamine release in the striatum causes long-term linkage of connections between recently active glutamate inputs and GABAergic output neurons. These synaptic adaptations are the neural basis of associative memory between reward-predicting cues and subsequent rewards; they are the mechanism by which these cues come to guide sequences of reward seeking.

## Low Dopamine Levels Are Aversive

Reduced activity in a large subset of dopaminergic projections to the ventral striatum is associated with aversion. Optogenetic inhibition of ventral tegmental area dopamine neurons produces avoidance of associated places and cues, an effect that depends on D<sub>2</sub> receptor signaling (Danjo et al. 2014, Ilango et al. 2014). Inhibition of these neurons via D<sub>2</sub> receptor activation causes a conditioned place aversion and mediates negative affect (Liu et al. 2008). Aversive stimuli of various sensory modalities broadly inhibit dopamine release in the ventral striatum (de Jong et al. 2018, Menegas et al. 2018). These studies are consistent with reports that aversive stimuli preferentially activate a subset of D<sub>2</sub>-expressing striatal output neurons (Xiu et al. 2014), and they provide causal evidence that reductions in striatal dopamine are aversive.

Rat vocalizations confirm that drug self-administration is pleasant. During cocaine self-administration or when morphine is given, rats increase high-frequency (~50-kHz) vocalizations that are associated with pleasurable stimuli; low-frequency (22-kHz) vocalizations dominate when aversive stimuli or opiate antagonists are given (Haney & Miczek 1994, Scardochio et al. 2015). During cocaine testing, when experimenter-administered doses are programmed at lower doses or lower frequency than what animals would normally self-select, 22-kHz vocalizations are prevalent; when higher than normal cocaine doses are given, 50-kHz vocalizations appear and 22-kHz vocalizations decrease (Barker et al. 2010, 2014).

When a rat is repeatedly exposed to a flavored saccharin solution that is not followed immediately by cocaine but that precedes a distant cocaine self-administration session, the taste of this normally rewarding saccharin solution reduces phasic dopamine release in the ventral striatum, becomes aversive, and alters striatal neural activity in a manner similar to the effects of quinine (Wheeler et al. 2008, 2011, 2015). The saccharin becomes aversive, as demonstrated in a taste-reactivity test where infusing the solution into the animal's mouth induces gaping and ejection of the solution, the same responses seen when quinine is injected. By contrast, if the saccharin solution predicts immediate drug delivery or delayed access to saline self-administration, it elicits licking and swallowing, the normal responses to sweet substances. The strength of the learned aversion to saccharin that predicts delayed cocaine self-administration is correlated with early-session drug taking; rats that show more aversive responses to the conditioned taste subsequently self-administer more cocaine (Wheeler et al. 2008). A similar correlation between degree of aversion and amount of subsequent drug taking has been shown with other addictive drugs (Wise et al. 1976). After the drug-seeking response has been largely extinguished (during several cocaine-free extinction sessions), presentation of the delayed cocaine predictive taste cue reinstates the seeking behavior, doubling responses to the partially extinguished cues for immediate drug delivery. Presentation of unconditioned saccharin in control animals does not increase responding (Wheeler et al. 2015).



Presentation of unconditioned quinine—which also reduces dopamine and creates an aversive state—similarly reinstates (or sets the stage for reinstatement) of cocaine seeking. Release of the stress hormone corticotropin-releasing factor (CRF) (Zorrilla et al. 2014) is one source of dopamine inhibition. Microinjections of a CRF receptor antagonist into the region of dopamine cell bodies attenuates part of the dopaminergic inhibition and blocks drug seeking (Twining et al. 2015).

In humans, cocaine-predictive cues are clearly aversive when presented in the absence of the drug. They increase self-reported indexes of anger, confusion, tension, and depression (Robbins et al. 2000). They cause anxiety, engage physiological stress systems, and induce a reportedly negative affective craving state (Blaine et al. 2018). The physiological impact of drug-predictive cues is often similar to that evoked in humans by stressful stimuli or imagery (Sinha 2008). Thus, one of the suggested motivators of drug seeking in addicts is a desire to alleviate a cue-induced negative affective state.

Animals learn to avoid cues that predict the unavailability of addictive drugs, yet the brain mechanisms by which this happens are not well understood. In the course of developing drug-seeking habits, many aspects of brain function are adjusted (Lüscher & Malenka 2011, Nestler 2013). What remains to be clarified is which of these central events cause drug taking and which are only consequences (Wise & Koob 2014).

### **Tonic Dopamine Release Determines Motivational Arousal**

Pacemaker firing of the dopamine system—repeated independent discharges—is also important and plays a role in motivational arousal. Motivational arousal reflects the willingness to exert effort for a reward (Correa et al. 2002, Salamone et al. 2007, Wise 1987). Pacemaker firing refers to a series of individual discharges, triggered by a slow depolarizing current within the dopaminergic neurons (Grace 1991). The neurons discharge somewhat irregularly (discharge rate is also influenced by variations in GABA-mediated inhibition) at 3–8-Hz frequency with interspike intervals approximately three times longer than those seen in burst firing (Grace & Bunney 1984b). Dopamine is released from multiple sites along the length of dopamine axons (Liu et al. 2018), few of which show synaptic contacts (Yung et al. 1996). It diffuses from release sites to act largely by volume transmission (Agnati et al. 2010) at distant receptors. Unlike phasic dopamine peaks, it is measured at approximately the same level throughout the striatum. Because dopamine cannot invade areas of equal or higher concentration, it must be inactivated by reuptake or metabolism rather than by diffusion.

**Tonic activation is measured by microdialysis.** Dopamine levels maintained by pacemaker (single-impulse) firing are below the detection threshold for FSCV (detection threshold is ~20 nM) (Owesson-White et al. 2012). They can be detected by microdialysis, which has the sensitivity to detect dopamine levels as low as 0.1 nM (Westerink et al. 1987b). Pacemaker firing maintains dopamine levels in the range of ~2–10 nM. Whereas microdialysis does not differentiate the contributions from pacemaker firing and burst firing, the effects of burst firing have limited effects on microdialysis measurements because they are relatively infrequent and are distributed along the large surface of the microdialysis probe.

**Tonic firing is normally modulated by hormones and peptides.** In the normal environment, many factors—but not environmental stimuli (Schultz 1997)—can regulate the pacemaker firing of the dopamine system (Hsu et al. 2018). The system is controlled, for example, by stress (Wang et al. 2005) as well as feeding-related hormones (You et al. 2018) that act on dopaminergic neurons



or their inputs including leptin (Figlewicz et al. 2003, Fulton et al. 2006, Leinninger et al. 2009), insulin (Figlewicz et al. 2003), GLP-1 (Alhadeff et al. 2012), and ghrelin (Jerrhag et al. 2011). Hormones and peptides contribute to the control of the dopamine system by slow actions on dopamine neuron receptors altering the rate of pacemaker firing or by actions through GABA neurons (the inhibitory controllers of the dopamine system), which also influence the rate of tonic firing but do not cause burst firing.

**Tonic firing determines motivational arousal.** The contributions of dopamine released by pacemaker firing can be estimated in animals at rest under minimal stimulus conditions (Campbell & Sheffield 1953). Measured using two methods—no-net-flux and extrapolation to zero flow—baseline dopamine release in sated freely moving animals is  $\sim 4.2$  nM in the ventral stratum (Parsons & Justice 1992). Blocking phasic dopaminergic activation by blocking either dopamine synthesis or packaging of dopamine into releasable vesicles establishes animals with no noticeable motivational arousal (Szczyepka et al. 1999, Zhou & Palmiter 1995). By contrast, replacing dopamine or giving an immediate dopamine precursor restores it (Heusner et al. 2003, Szczyepka et al. 2001, Zhou & Palmiter 1995). Depletion of dopamine by neurochemical lesions has the same effect as dopamine depletion (Ungerstedt 1971). The use of dopamine antagonists to reduce dopamine in trained animals produces the clearest evidence of decreased motivational arousal. These animals expend less energy in partial or progressive ratio schedules, reducing the effort they are willing to expend for a given reward (Salamone et al. 2007). In patients with Parkinson's disease, where dopamine levels are significantly decreased, both speed of hand movements in a placement task (Mazzoni et al. 2007) and willingness to squeeze a dynamometer decreased (Chong et al. 2015); when the patients were back on medication, squeezing increased (Chong et al. 2015). Together, these studies suggest that pacemaker dopamine release determines motivation rather than the ability to work for reward.

Conversely, elevating dopamine levels above baseline increases motivational arousal. Low doses of amphetamine have this effect (Wyvell & Berridge 2000), as does sensitizing the system by prior amphetamine experience (Wyvell & Berridge 2001). In a study with an inducible dopamine transporter knockdown that increased pacemaker firing but failed to alter burst firing, animals showed increased lever pressing for food in a progressive ratio task and increased choice for a more palatable food in a choice paradigm (Cagniard et al. 2006). A dopamine uptake inhibitor that doubled baseline dopamine levels increased willingness to ignore normal pellets and to work for high-carbohydrate pellets (Yohn et al. 2016). A low dose of amphetamine caused humans to increase effort for monetary rewards (Wardle et al. 2011).

In each case, decreased baseline dopamine levels are associated with decreased willingness to exert effort, and stimulation of the dopamine system reverses this effect. Although dopamine depletion attenuates responsiveness to predictive cues, it does not attenuate responsiveness to food (Ikemoto & Panksepp 1996). Dopamine is important for the motivation of seeking responses, but is not important for the unconditioned responses to the food or punisher. Dopamine levels represent a constantly updating signal about the value of a given situation, influencing the willingness to work to obtain reward (Hamid et al. 2016).

## **Dopamine Receptors Are Downregulated by Habitual Reward Seeking**

Surface expression of D<sub>2</sub> dopamine receptors is decreased by long-term self-administration of addictive drugs such as opiates (Wang et al. 1997), cocaine (Nader et al. 2006, Volkow et al. 1993), methamphetamine (Volkow et al. 2001), alcohol (Volkow et al. 2007), and nicotine (Wiers et al. 2017). This effect also results from compulsive overeating (Johnson & Kenny 2010,

Volkow et al. 2008). D<sub>2</sub> receptors have high affinity for dopamine, and resting dopamine levels in the striatum keep these receptors frequently occupied. D<sub>1</sub> receptors have low affinity for dopamine and are activated primarily by high concentrations (burst firing) of dopaminergic neurons. Thus, it is not surprising that dramatic changes in D<sub>2</sub> receptor expression result from habitual activation. Conflicting evidence suggests that D<sub>1</sub> receptors are also decreased by habitual addictive drug use (Thanos et al. 2017).

Leaving potentiated habits strong, long-term decreases in dopamine receptor expression result in decreased sensitivity to the range of rewarding stimuli that are not already potentiated as part of established habits. Because such decreases are seen in obese individuals, a common mechanism may link overconsumption of energy-rich foods with addiction. The selective decrease in dopaminergic responsiveness to nonhabitual stimuli—measured by decreased expression of dopamine receptors—offers an interesting measure of addiction that extends dopamine beyond simple addiction to drugs.

## **ADDICTIVE DRUGS**

### **Addictive Drugs Are Habit-Forming and Activate the Dopamine System**

Burst firing by predictive stimuli that lead animals to addictive drugs must be learned; it develops when stimuli reliably precede the burst firing triggered by unconditioned rewards. Hebb (1949) outlined a mechanism for the development of burst firing to predictors. This burst firing of dopaminergic neurons in response to unconditioned rewards establishes burst-firing responses to predictive stimuli that immediately precede unconditioned rewards as well as long-term potentiation of synapses between glutamate-containing sensory neurons and D<sub>1</sub> striatal output neurons. It also establishes long-term depression of synapses between glutamate-containing sensory neurons and D<sub>2</sub> striatal output neurons. Long-term potentiation and long-term depression (which also develops in other regions receiving dopamine input) establish relatively permanent response habits by which sequences of environmental stimuli lead the animal to the drug.

We also know, though in much less detail, that depression of the dopamine system becomes established for cues that predict delayed rewards. In the case of cocaine, cues predicting delayed access to cocaine become aversive (see above). Addicts work to avoid cues that predict these delays, and avoidance becomes increasingly established as the drug habit becomes progressively learned. Although the effects of drugs that predict future but not immediate cues have not been tested with other addictive drugs, it seems likely that the effects of cocaine will prove true for other drugs.

Here we consider whether and how each of the main addictive drugs activates the dopamine system. Although cocaine, amphetamine, opiates, alcohol, nicotine, cannabis, barbiturates, and benzodiazepines activate the dopamine system, they do so to different degrees. Caffeine at high doses activates the dopamine system but has its own intracellular, dopamine-like, low-dose effects. High-energy foods, and perhaps the thrills of gambling, also activate the dopamine system and do so at levels that should cause burst responding.

### **Cocaine**

Cocaine is a psychomotor stimulant. Cocaine and amphetamine are differentiated from the traditional stimulants strychnine, pentylenetetrazol, and picrotoxin that produce convulsions and are not addictive. Cocaine elevates extracellular dopamine levels (Di Chiara & Imperato 1988) and is habit-forming (Deneau et al. 1969). It causes a form of euphoria that overlaps with amphetamine euphoria but is quite distinct from the euphoria attributed to other drugs. Cocaine's stimulant effect increases behavior and mood and alleviates boredom and fatigue (Jones 1984).

Cocaine activates the dopamine system by blocking the reuptake of dopamine by the dopamine transporter, a molecule expressed by dopaminergic neurons. It also blocks the uptake of two other neurotransmitters: norepinephrine and serotonin. Cocaine has aversive as well as rewarding effects; its aversive effects may be due to cocaine's blockade of the norepinephrine or serotonin transporter. Correlates of the aversive events, including activation of their predictors, are relayed to the lateral habenula nucleus, which trans-synaptically inhibits the dopamine system (Jhou et al. 2013). Of the various projections of the dopamine system the projection to the dorsal striatum seems most important for habit formation (Szczypka et al. 2001, Yin et al. 2004).

Cocaine elevates basal dopamine levels severalfold, as measured by microdialysis (Di Chiara & Imperato 1988). At self-administered doses, it elevates baseline striatal dopamine three- to fivefold (Ito et al. 2000, 2002; Weiss et al. 1992, Wise et al. 1995b). Cocaine makes accumulating peaks from burst firing (as measured by FSCV) more visible, driving peaks well above the 20-nM threshold in treated animals (Stuber et al. 2005). If dopamine systems are lesioned, then rats continue to respond for apomorphine (a postsynaptic dopamine agonist) but lose their willingness to respond for cocaine (a dopamine uptake inhibitor) (Roberts et al. 1977). Low doses of dopamine receptor antagonists cause rats to increase their response rate, taking more than normal doses of cocaine per hour; when high doses of antagonists are given, the rewarding effect of cocaine is blocked (de Wit & Wise 1977, Ettenberg et al. 1982). Within binges of cocaine self-administration, rats respond to the next injection whenever their extracellular dopamine levels fall to a threshold approximately double their normal baseline level (Wise et al. 1995b).

Cocaine-experienced animals learn not only about the rewarding effects of the drug, but also about aversive side effects of cocaine abstinence that occur with or after cocaine exposure. They learn to approach places where they have had immediate cocaine injections, and they avoid places where they have been placed 15 minutes after receiving cocaine injections (Ettenberg et al. 1999). Low doses of cocaine elicit increased 22-kHz vocalizations, indicative of aversion (Barker et al. 2014). Such aversive effects as adrenergic or serotonergic signaling may be caused directly by cocaine or its aftereffects that result from the prior wearing off of cocaine's positive effects (Wenzel et al. 2013). Rats also learn that cues paired with delayed access to cocaine are aversive (Grigson & Twining 2002, Wheeler et al. 2008). For example, the normally appetitive taste of saccharin elicits aversive behavioral reactions when it is repeatedly delivered over a 30- or 45-minute period prior to the opportunity to self-administer cocaine. By contrast, a taste cue that is paired with delayed access to saline self-administration has no such effect. The oral responses are similar to those elicited by unconditioned bitter tastes such as quinine: Rats gape and eject these solutions from their mouths. Once a taste becomes a conditioned aversive stimulus, decreasing striatal dopamine release, it has established an aversive state (Wheeler et al. 2011, 2015). It establishes a negative conditioning situation; it is relief from the aversive state—due to a cue that signals immediate cocaine—that appears to be reinforcing. The stress hormone CRF has been suggested (Baker et al. 2004, Koob 1999) as a source of the aversive state. Ventral midbrain microinjections of a CRF receptor antagonist partially block the ability of quinine to inhibit dopamine release (Twining et al. 2015). Understanding the way that cues of delayed or unavailable access modify anxiety and drug taking will be important for improving animal models of addiction, as these cues elicit behavioral responses closely aligned with those observed in human addicts (Robbins et al. 2000, Sinha 2008).

Cocaine-addicted humans develop long-term decreases in expression of D<sub>2</sub> dopamine receptors (Volkow et al. 1992), presumably leaving them with reduced sensitivity to nonhabitual rewards.

## Amphetamines

Amphetamine, methamphetamine, and related drugs are also psychomotor stimulants. They elevate dopamine levels (Di Chiara & Imperato 1988, Gough et al. 2014) and are habit-forming (Deneau et al. 1969, Pickens & Harris 1968). As with cocaine, the direct effects of amphetamines are elevated mood, increased alertness, and relief from fatigue, and their withdrawal symptoms are depressed activity, depressed mood, and lack of motivation. Animals learn to avoid cues that predict delayed access to amphetamine (Fudala & Iwamoto 1990).

Amphetamines elevate extracellular dopamine levels by releasing dopamine from vesicles and by reversing the dopamine transporter (Jones et al. 1998, Sulzer et al. 1995). Amphetamine causes rapid dopamine release. In a typical self-administration experiment, baseline dopamine is elevated several-fold (Ranaldi et al. 1999), accompanied by phasic dopamine release (Daberkow et al. 2013). Low doses of dopamine receptor antagonists cause increased amphetamine intake; high doses cause extinction responding (Wise et al. 1976, Yokel & Wise 1975).

As with cocaine-addicted individuals, methamphetamine-addicted humans develop long-term decreases in expression of D<sub>2</sub> dopamine receptors (Schrantee et al. 2015, Volkow et al. 2001), presumably leaving them with reduced sensitivity to nonhabitual rewards.

## Opiates

Opiates including morphine, heroin, codeine, fentanyl, and oxycodone are sedative hypnotics that indirectly (Johnson & North 1992) elevate dopamine levels (Di Chiara & Imperato 1988, Vander Weele et al. 2014), decrease tension and pain, and are habit-forming (Deneau et al. 1969). These drugs cause euphoria different from the euphoric effects of cocaine or amphetamine but with some degree of overlap with those caused by alcohol, benzodiazepines, and barbiturates (Kalant 1977).

Opiates have three classes of receptors. Actions at the  $\mu$ -opioid receptor, localized to the ventral tegmental area, are primary for the habit-forming effects of opiates (Bozarth & Wise 1981, Broekkamp et al. 1976). Rats will lever press for microinjections of the selective  $\mu$ -agonist DAMGO ([D-ALA<sup>2</sup>, N-Me-Phe<sup>4</sup>-Gly<sup>5</sup>-ol]-enkephalin) to this region, where it is two orders more effective than the  $\delta$ -agonist DPDPE ([D-Pen<sup>2</sup>, D-Pen<sup>5</sup>]-enkephalin) (Devine & Wise 1994). These compounds disinhibit the dopamine system with the same relative difference in potencies (Devine et al. 1993). Endogenous  $\mu$ -opioid endomorphin-1 is self-administered into this region (Zangen et al. 2002). Heroin is preferred for intravenous use. It enters the brain more quickly than does morphine, is quickly metabolized (losing its two acetyl groups), and becomes morphine as it enters the brain. It is self-administered and elevates dopamine levels to approximately the same extent as cocaine (Wise et al. 1995a).

The mechanism by which opiates activate the dopamine system is trans-synaptic. It inhibits GABA-containing neurons that, in turn, normally hold the dopamine neurons under inhibitory control (Sugita et al. 1992). Thus, morphine disinhibits the dopamine system (Johnson & North 1992) by an action on these (Johnson & North 1992) or nearby GABA neurons (Ikemoto et al. 1997, Jhou et al. 2012, Liu & Ikemoto 2007). The most recent evidence suggests that heroin selectively disinhibits a medial subgroup of dopamine neurons that project to the medial shell of the ventral striatum (Corre et al. 2018).

Mice learn not only to approach cues that predict reward, but also to avoid cues that predict conditions where opiates will not be available (Zhu et al. 2016). Opiates have multiple behavioral effects: They alleviate pain (Tung & Yaksh 1982), stimulate feeding (Pecina & Berridge 2005), and alleviate social distress (Herman & Panksepp 1978). They have at least two forms of direct aversive effects. First, they have direct aversive opiate effects in the periphery (Bechara & van der Kooy

1985) mediated by the  $\kappa$ -opioid receptor. Second, they have aversive effects at  $\kappa$ -opioid receptors within the brain (Bals-Kubik et al. 1989, Hawes et al. 2017).

As with cocaine- and methamphetamine-addicted users, opiate-addicted humans develop long-term decreases in expression of D<sub>2</sub> dopamine receptors (Wang et al. 1997), presumably leaving them with reduced sensitivity to nonhabitual rewards.

## Alcohol

Alcohol is a depressant drug, but at low doses and early during intoxication, it elevates striatal dopamine levels and is habit-forming. The immediate effects of low doses or early intoxication are euphoria and a decrease in inhibitions; when higher doses are taken, depression is experienced.

Alcohol activates the dopamine system (Di Chiara & Imperato 1986). Self-administered doses increase resting dopamine levels by approximately 50% over normal baseline in alcohol-preferring rats (Weiss et al. 1992). Alcohol causes minor increases in baseline dopamine levels. However, FSCV reveals alcohol-induced dopamine peaks, the product of dopaminergic burst firing, in some striatal subregions (Robinson et al. 2009), but the mechanisms by which it does so are not well understood (Abraham et al. 2017). Unlike other addictive drugs, it has no receptor and thus does not have a single or simple mechanism of action. It binds to several ion channels on multiple receptors. A strong possibility is that the ability of alcohol to activate the dopamine system depends on interactions with glycine receptors that interact with GABA receptors in the ventral striatum or ventral tegmental area (Söderpalm et al. 2017). Alcohol may also activate the reward system by activating serotonin-3 receptors (McBride et al. 2004) on dopaminergic neurons (Wang et al. 2019). Alcohol self-administration is also reduced by mecamylamine, a nicotinic receptor blocker (Ericson et al. 1998), suggesting alcohol has multiple sites of rewarding action.

Although the taste of alcoholic beverages is usually aversive to new users, alcohol-associated cues cause persistent craving, anxiety, and behavioral distress in experienced users (Sinha et al. 2009). As with habitual cocaine-, methamphetamine-, and opiate-addicted users, alcoholic humans develop long-term decreases in expression of D<sub>2</sub> dopamine receptors (Volkow et al. 2017, Yoder et al. 2016), presumably leaving them with reduced sensitivity to nonhabitual rewards.

## Nicotine

Nicotine is a psychomotor stimulant that causes burst firing of dopamine neurons (Grenhoff et al. 1986), elevates extracellular dopamine levels (Di Chiara & Imperato 1988, Doyon et al. 2013, Fu et al. 2000), and is habit-forming (Cohen & Ettenberg 2007, Corrigall et al. 1992, Donny et al. 1995). It acts at a subset of acetylcholine receptors in the brain, with actions in both the ventral tegmental area (Picciotto et al. 1998) and striatum (Jones et al. 2001, Reuben & Clarke 2000).

Nicotine acts at subsets of acetylcholine receptors that are expressed in many brain regions; different subsets are composed of different subunit combinations (McGehee & Role 1995). The primary nicotinic dopamine-elevating action involves receptors localized in the medial portion of the ventral tegmental area (Ikemoto et al. 2006, Miller et al. 2005, Picciotto et al. 1998), but it can also act at receptors in the striatum (Mifsud et al. 1989). Each of these receptor groups regulates the release of dopamine from dopaminergic axon terminals (Champtiaux & Changeux 2004, Salminen et al. 2004). Nicotine causes dopaminergic neurons to discharge, and nicotinic effects in the striatum involve a mixture of effects that influence release of dopamine from axon terminals (Rice & Cragg 2004, Windels & Kiyatkin 2003, Zhang & Sulzer 2004). Cigarette smoking also increases dopamine levels through non-nicotinic substances by inhibiting the catabolic enzyme monoamine oxidase (Smith et al. 2016).

Although nicotine is rewarding, its prominent subjective effect for new users is aversive. If nicotine is given after a 20-minute delay, the cues that were present during the delay become aversive (Fudala & Iwamoto 1987).

As with habitual cocaine-, methamphetamine-, opiate-, and alcohol-addicted users, nicotine-addicted humans develop long-term decreases in expression of D<sub>2</sub> dopamine receptors (Fehr et al. 2008), presumably leaving them with reduced sensitivity to nonhabitual rewards.

## **Marijuana**

The addictive agent in marijuana is  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC). It is a depressant and causes relaxation and a form of euphoria that overlaps to some extent with, but is clearly different from, opioid euphoria. It acts at cannabinoid receptors in the brain (Matsuda et al. 1990), is habit-forming (Curran et al. 2016, Gardner & Lowinson 1991), and elevates extracellular dopamine levels (Chen et al. 1990, Lupica & Riegel 2005, Oleson & Cheer 2012). THC also increases dopamine signaling in the human striatum (Bossong et al. 2009). The growth of marijuana for human use has become complicated by recent changes in legislation and by the high concentrations of  $\Delta^9$ -THC that have recently become available. Because of delay of absorption, awareness that an overdose has been taken orally is likely to be more impaired than when the substance is smoked.

CB1 and CB2 are receptors for the two endogenous cannabinoids anandamide and 2-arachidonoylglycerol that function as retrograde neurotransmitters. They have an atypical mechanism of action. They are synthesized and released by dopaminergic neurons and elsewhere, and they act presynaptically on local axon terminals (Davis et al. 2018, Mateo et al. 2017). Glutamate and GABA terminals are each targets for these transmitters; they are found near the dopamine cell bodies where they can activate dopamine neurons or inhibit local GABA cells that inhibit dopamine neurons (Freund et al. 2003, Ng Cheong Ton et al. 1988, Riegel & Lupica 2004, Sperlagh et al. 2009). The net result of cannabinoid treatment is increased burst firing of dopamine neurons (French et al. 1997) and increased dopamine efflux into the striatum and prefrontal cortex (Chen et al. 1991, Ng Cheong Ton et al. 1988, Oleson & Cheer 2012). At high doses, cannabis also acts at CB2 receptors that are expressed on dopaminergic neurons (Garcia et al. 2016, Spiller et al. 2019). Not only are cannabinoids rewarding, but pharmacological blockade of the CB1 cannabinoid receptor also inhibits the rewarding effects of nicotine, ethanol, morphine, heroin (Manzanares et al. 2018, Oleson & Cheer 2012), and food seeking (Abel 1975, Foltin et al. 1986, Kirkham 2005).

In rodents, abrupt cessation of THC does not produce an obvious withdrawal state. However, precipitated withdrawal via treatment with a CB1 receptor antagonist does and is associated with reduced dopamine signaling (Diana et al. 1998). The observed withdrawal symptoms in humans following THC cessation are decreased appetite, irritability, nervousness, restlessness, shakiness, sleeping difficulty, stomach pain, strange dreams, sweating, and weight loss (Budney & Hughes 2006).

As with habitual cocaine, methamphetamine, opiate, nicotine, and alcohol use, human addicts with psychotic symptoms develop long-term decreases in expression of D<sub>2</sub> dopamine receptors (Bloomfield et al. 2014, Fehr et al. 2008). With an unusually sensitive assay, cannabis users without such symptoms have downregulated D<sub>2</sub> receptors (van de Giessen et al. 2017), presumably leaving them with reduced sensitivity to nonhabitual rewards.

## **Barbiturates and Benzodiazepines**

Barbiturates and benzodiazepines are depressants producing withdrawal symptoms that overlap with those associated with ethanol (Kalant 1977). Although their primary action is depressant, they

activate (disinhibit) the dopamine system. They elevate dopamine levels (Di Chiara & Imperato 1986, O'Brien & White 1987, Schelp et al. 2018, van der Kooij et al. 2018) and are habit-forming (Griffiths et al. 1981). The dopamine-activating effects of these drugs appear to be dose dependent; low doses cause obvious dopamine-like behavioral actions (Wise & Bozarth 1987). Abrupt withdrawal from barbiturates can also cause convulsions (Essig 1966).

## Caffeine

Caffeine is a psychomotor stimulant that is habit-forming. It produces feelings of well-being, happiness, alertness, and sociability (Griffiths et al. 2003). At high doses, it can elevate dopamine levels (Acquas et al. 2002, Okada et al. 1997, Okada et al. 1996). However, at the doses humans usually consume, caffeine is minimally effective at activating the dopamine system. At low doses, it blocks the effects of adenosine at adenosine receptors that reside on dopamine-sensitive output neurons of the striatum (Ferre 2016, Fredholm et al. 1999).

Caffeine is a particularly interesting substance for addiction research. It is marginally rewarding, and despite many laboratory attempts, intravenous caffeine is not self-administered in animals. Unless questioned, most human users are not aware of its effects on mood. Caffeine potentiates the rewarding effects of alcohol and nicotine (Rezvani et al. 2013) as well as nondrug reinforcers (Sheppard et al. 2012). Caffeine blocks adenosine  $A_{2A}$  receptors and forms heteromers with  $D_2$  dopamine receptors in  $D_2$  striatal output neurons (Ferre et al. 2008). Furthermore, caffeine increases postsynaptic dopamine transmission by blocking adenosine  $A_1$  receptors that form heteromers with  $D_1$  receptors in  $D_1$  striatal output neurons (Ferre 2016). Thus, caffeine has intracellular effects that are dopamine-like and has the potential to influence long-term potentiation and depression (Costenla et al. 2010). Withdrawal from caffeine use has clinical symptoms that overlap with those of anxiety, depression, and insomnia (Meredith et al. 2013). Acute caffeine exposure induces changes in  $D_2$  receptor ligand binding potential in the striatum (Volkow et al. 2015), which is probably related to allosteric interactions in the  $A_{2A}$ - $D_2$  receptor heteromer (Bonaventura et al. 2015).

## Other Forms of Addiction

When the terms “addict” and “addiction” were first borrowed from Latin, they referred generally to self-imposed habits. The terms became frequently associated with addictive drugs approximately one century ago. Today, it is widely assumed that drug addiction is the defining example of addiction, and the question has become whether habitual gambling, eating of high-energy foods, or seeking of some other potent reward qualifies as addiction.

A strong case for generalizing the terms comes from consideration of compulsive overeating. As with drug-seeking behaviors, food-seeking habits are lost when dopamine is depleted from the brain (Zhou & Palmiter 1995) and are restored when the ability to synthesize dopamine is restored to the dorsal striatum (Szczycka et al. 2001). Consumption of, or lever pressing for, normal lab chow doubles dopamine levels (Hernandez & Hoebel 1988); consumption of sucrose alone (Hajnal et al. 2004) or corn oil alone (Liang et al. 2006) has approximately half this effect. Food reward causes burst firing and phasic dopamine release, and it establishes long-term potentiation and depression. Motivation to feed—sensitivity to food-predictive stimuli—is controlled by phasic activation of the dopamine system. Activation is influenced by hormones that control appetite and satiety including ghrelin, GLP-1, leptin, and insulin. All these factors interact with motivation for cocaine (You et al. 2016, You et al. 2018), and some interact with motivations for drug taking (Engel & Jerlhag 2014). As with habitual cocaine, methamphetamine, opiate, nicotine, and cannabis users,



humans who overconsume high-energy foods have decreased expression of D<sub>2</sub> dopamine receptors (Volkow et al. 2008, Wang et al. 2001), presumably leaving them with reduced sensitivity to nonhabitual rewards.

Pathological gambling has recently been classified as an addictive disorder. Gamblers have higher rates of dopamine turnover than do nongamblers, as reflected by elevated dopamine metabolites in cerebrospinal fluid (Bergh et al. 1997). Increased dopamine signaling is correlated with increased impulsivity, a risk factor for both gambling and substance abuse disorders (Clark et al. 2012). Periods of maximal uncertainty of reward delivery cause sustained activation of the dopamine system (Fiorillo et al. 2003). Furthermore, use of dopamine receptor agonists is associated with increased gambling (Moore et al. 2014, Potenza et al. 2013). However, positron emission tomography studies of dopamine receptor binding do not show differences between pathological gamblers and healthy controls (Potenza et al. 2013). Compulsive overeating and gambling suggest that the ability to establish dominant reward-seeking habits varies across the range of reinforcing stimuli and extends beyond the drugs that have dominated the recent literature.

### SUMMARY POINTS

1. The definition of addiction as a very strong habit applies to the use of cocaine, amphetamines, opiates, alcohol, nicotine, marijuana, barbiturates, benzodiazepines, caffeine, energy-rich foods, and, perhaps, gambling and other behaviors.
2. In each case, the reward activates the dopamine system, causing burst firing or the equivalent dopamine level, long-term potentiation of associations with predictive cues, and decreases in cell-surface expression of dopamine receptors.
3. This definition of addiction identifies rewards and reward-predictive cues (of motivation or aversion) as what control behavior. It also extends the definition to cases involving nondrug rewards.
4. This definition suggests that motivational level depends on the rate of pacemaker firing in the dopamine system.

### FUTURE ISSUES

1. The aversion that develops to cues that predict future (but not immediate) drugs has been determined with only one kind of cue and one addictive drug. While it seems most likely that other drugs will have the same effect, this should be tested. There are likely to be differences in the rates of aversion learning in response to such cues, and between-drug comparisons should be made.
2. Do cues other than taste—do lights, sounds, or odor cues, for example—become aversive through similar conditioning?
3. How does the aversive state caused by cues for access to future drug influence subsequent drug seeking? How does the aversive taste cue instigate approach to reward-seeking cues, which involves activation of D<sub>1</sub> neurons and perhaps depression of D<sub>2</sub> neurons? One possibility is that the aversion-induced reduction in striatal dopamine causes a subsequent rebound of dopamine release that drives seeking behavior. Another possibility

is that while the dominant response is depression of dopamine release from most striatal terminals, another subset of dopamine neurons is concurrently activated by residual predictive cues and guides reinstatement.

4. How do aversive drug cues affect dopamine signaling in brain regions other than the striatum, such as the prefrontal cortex, amygdala, and hippocampus?
5. Microdialysis and fast-scan cyclic voltammetry have been used in separate experiments; they have not been used concurrently in the same animals. Concurrent measurements by the two methods—comparing resting conditions with conditions of motivation (by food deprivation or by exposure to drug-predictive cues)—should help clarify our understanding of dopamine fluctuations under low and intermediate levels of motivation.
6. How do dopamine fluctuations influence subsets of striatal output neurons? Imaging of calcium indicators should be used to further characterize the effects of dopamine concentration on subpopulations of D<sub>1</sub>- vs D<sub>2</sub>-expressing output neurons. The tools for this kind of analysis have only recently been developed, and such studies may already be in progress.

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