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Consolidating the Circuit Model for Addiction

Christian Lüscher[1,2] and Patricia H. Janak[3,4]

[1]Department of Basic Neurosciences, Faculty of Medicine, University of Geneva, CH-1211 Geneva, Switzerland; email: Christian.Luscher@unige.ch

[2]Clinic of Neurology, Department of Clinical Neurosciences, Geneva University Hospital, CH-1211 Geneva, Switzerland

[3]Department of Psychological and Brain Sciences, Krieger School of Arts and Sciences, Johns Hopkins University, Baltimore, Maryland 21218, USA

[4]The Solomon H. Snyder Department of Neuroscience, Johns Hopkins School of Medicine, Baltimore, Maryland 21205, USA

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Abstract

Addiction is a disease characterized by compulsive drug seeking and consumption observed in 20–30% of users. An addicted individual will favor drug reward over natural rewards, despite major negative consequences. Mechanistic research on rodents modeling core components of the disease has identified altered synaptic transmission as the functional substrate of pathological behavior. While the initial version of a circuit model for addiction focused on early drug adaptive behaviors observed in all individuals, it fell short of accounting for the stochastic nature of the transition to compulsion. The model builds on the initial pharmacological effect common to all addictive drugs—an increase in dopamine levels in the mesolimbic system. Here, we consolidate this early model by integrating circuits underlying compulsion and negative reinforcement. We discuss the genetic and epigenetic correlates of individual vulnerability. Many recent data converge on a gain-of-function explanation for circuit remodeling, revealing blueprints for novel addiction therapies.

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INTRODUCTION

The compulsive nature of drug seeking and consumption defines drug addiction (Am. Soc. Addict. Med. 2011). Addicts lose control over their consumption, which continues unabated despite major negative consequences. These consequences may include economic strain and also social withdrawal, with alienation from family members and isolation from friends. At this stage, the consumption of the drug no longer elicits pleasure, but it takes up most of the energy of the addict. Eventually, conflicts with the law and incarceration may occur. These negative consequences, however, will still not stop the search for the drug. In fact, addicts can develop elaborate plans to obtain the drug, demonstrating a very goal-directed yet unduly narrow behavioral scope. With strong willpower and support, addicts may withdraw from consumption, yielding to an aversive state that can be very painful, particularly with opioids. The withdrawal syndrome defines the dependence to the drug, and its avoidance by resuming drug intake is referred to as negative reinforcement (Koob 2020).

Addiction is a multifaceted disease of which only some key components can be modelled in animals. Since the general features of reward circuitry are common across model organisms (Scaplen & Kaun 2016), dopamine (DA)-dependent reinforcement and place preference to cocaine is observed in animals ranging from *Drosophila* to honey bees (Søvik et al. 2014) and rodents. Cocaine also leads to chemosensory cue conditioning in *Caenorhabditis elegans* (Musselman et al. 2012), and alcohol exposure creates special forms of memory in *Drosophila* that control drug consumption (Scaplen et al. 2020). Most of the research discussed here comes from experiments with rodents, initially carried out in rats, that typically used a behavioral pharmacology approach. Over the last two decades, the focus has shifted to favor mice because of the ease of genome editing. Positive reinforcement as well as initial drug adaptive behavior, such as locomotor sensitization, conditioned place preference, and cue-associated seeking, just to name a few, can reliably be observed in both rats and mice. Thanks to a myriad of Cre-driver lines (**http://www.credrivermice.org/**), cell type–specific observations and manipulations have enabled a circuit interrogation with unprecedented precision.

Conditioned place preference: a form of conditioning used to measure the motivational effects attributed to the environment in which addictive drugs are administered

In 2016, we reviewed the literature corroborating the emergence of a circuit model of addiction (Lüscher 2016) (**Figure 1**). The model was based on the defining commonality of addictive drugs: They increase mesolimbic DA levels (Di Chiara & Imperato 1988, Lüscher & Ungless 2006). We argued that the modulatory role of DA on glutamate transmission evokes forms of drug-adaptive

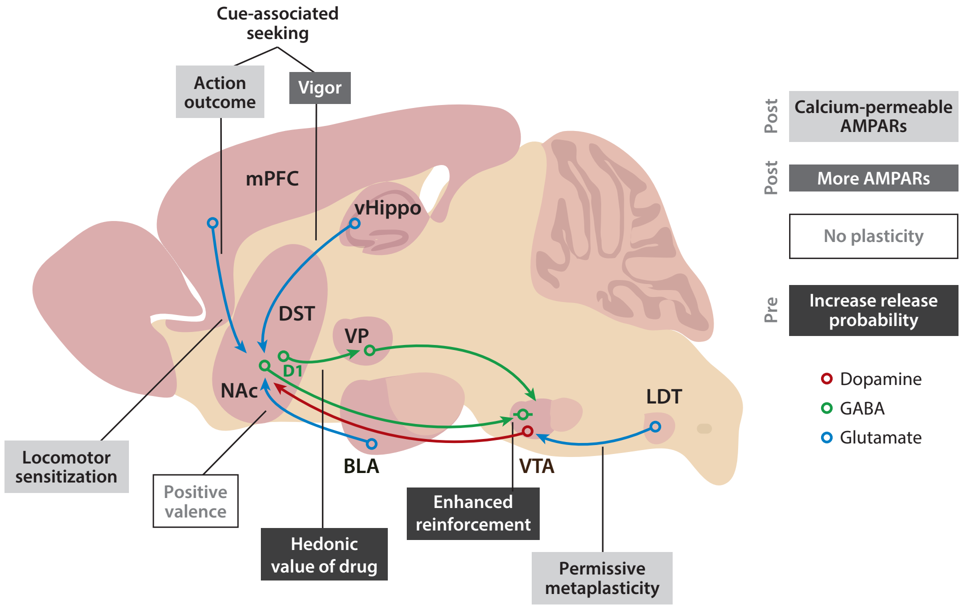

Figure 1

Circuits of positive reinforcement driving early drug adaptive behavior. DA neurons receive excitatory and inhibitory inputs from LDT and VTA GABA interneurons, respectively. The projection to the NAc is strongly reinforcing, most prominently by modulating cortical afferents from the mPFC that impinge onto D1R-expressing MSNs, which project back onto VTA GABA interneurons. Starting with the first exposure to an addictive drug, these circuits undergo drug-evoked synaptic plasticity, expressed by pre- and postsynaptic mechanisms in GABAergic and glutamatergic synapses, respectively. Insertion of calcium-permeable AMPARs in VTA DA neurons gates subsequent plasticity in NAc and on the midbrain projection of MSNs to enhance reinforcement, cause locomotor sensitization, and trigger cue-associated reinstatement. Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BLA, basolateral amygdala; D1R, dopamine receptor 1; DA, dopamine; DST, dorsal striatum; GABA, γ-aminobutyric acid; LDT, lateral dorsal tegmentum; mPFC, medial prefrontal cortex; MSN, medium spiny neuron; NAc, nucleus accumbens; vHippo, ventral hippocampus; VP, ventral pallidum; VTA, ventral tegmental area. Figure adapted from Lüthi & Lüscher (2014).

plasticity in many synapses. This is a staged process that starts in the ventral tegmental area (VTA) proper within hours of the first exposure (Ungless et al. 2001), before expanding, with time and repetitive exposure, to the nucleus accumbens (NAc) (Mameli et al. 2009). Through genetic, pharmacological, and optogenetic manipulations, many groups have established links of causalities between this process and early drug adaptive behaviors that are typically observed in all individuals (reviewed in Lüscher 2016). For example, selective depotentiation of excitatory afferents onto dopamine receptor 1 expressing–medium spiny neurons (D1R-MSNs) in the NAc abolishes cue-associated seeking behavior (Pascoli et al. 2012).

Even though the initial model offered mechanistic insight into how drugs usurp circuits of reward and motivation to change behavior, it had several shortcomings. First, it was based exclusively on excessive positive reinforcement without taking into account that avoidance of the very aversive withdrawal state also drives the transition to compulsion (Koob 2020). The contribution of such negative reinforcement is particularly visible for opioids and alcohol, which cause a strong withdrawal syndrome. Second, the model did not account for the stochastic nature of compulsion (Lüscher et al. 2020). It fell short of integrating why some individuals lose control while the

Ventral tegmental area (VTA): a nucleus at the dorsal tip of the brain stem with dopamine projection neurons

Nucleus accumbens (NAc): a nucleus of the ventral striatum integrating dopamine inputs from VTA and glutamate projections from prefrontal cortex, amygdala, and ventral hippocampus

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majority can use drugs recreationally. Finally, the model did not integrate additional modulatory systems such as serotonin signaling, which may actually counteract the transition to compulsion (Pelloux et al. 2012).

γ-Aminobutyric acid (GABA): a major inhibitory neurotransmitter

Here, we briefly review the initial version of the model and then address the three limitations listed above: (*a*) contribution of negative reinforcement, (*b*) stochastic transition to compulsion, and (*c*) modulation by additional transmitter systems. We also review the impact of the model on therapeutic approaches, which to date—alas—still remain limited. While much progress has been achieved, we close with a series of open questions that we hope will inspire future research on drug addiction, a disease representing a huge burden for society.

PHARMACOLOGICAL COMMONALITY OF ADDICTIVE DRUGS

The DA hypothesis posits that the reinforcing properties of addictive drugs stem from their effect on the mesolimbic DA system. All addictive drugs that have been tested increased DA levels in the NAc [but only minimally in the dorsal striatum (DST)] as measured with brain microdialysis in rats (Di Chiara & Imperato 1988). Novel tools to visualize DA release in the NAc and specific circuit manipulations confirm the involvement of the VTA-to-NAc projection of the mesolimbic DA system in drug reinforcement. When exposed to cocaine or heroin, the genetically encoded sensor combining a modified DA receptor fused to a circularly permutated gCAMP (D-light1) (Patriarchi et al. 2018) shows a strong fluorescent transient. Similar experiments currently carried out with additional addictive drugs confirm that strong rises in accumbal DA levels are common to all of them, as predicted by the DA hypothesis (Di Chiara & Imperato 1988). Giving a rat or mouse the opportunity to activate a laser to self-stimulate VTA DA neurons previously transfected with an optogenetic actuator is strongly reinforcing (Pascoli et al. 2015, Witten et al. 2011), and so is the self-inhibition of VTA γ-aminobutyric acid (GABA) neurons by shining an amber light onto these cells after transfection of an optogenetic inhibitor (Corre et al. 2018). Both behaviors are readily inhibited or occluded when heroin is injected. Conversely, chemogenetic inhibition of VTA DA neurons reduces heroin self-administration. The disinhibitory motif within the VTA is confirmed by monitoring calcium levels (as a proxy of neural activity) with genetically encoded fluorophores. When heroin is injected, GABA neurons are inhibited, while DA neurons become more active. These observations collectively demonstrate the behavior-reinforcing properties of DA, including during the self-administration of abused drugs.

A majority of DA neurons appear to encode reward prediction errors (RPEs) via their burst activity, which mediates error-driven learning, as described in temporal difference–reinforcement learning models (Schultz et al. 1997). This role of DA as a teaching signal provides a framework to understand how the strong, sustained impact of abused drugs on mesolimbic DA may set in motion the neurobiological changes underlying the transition to addictive behavior (Keiflin & Janak 2015, Redish 2004). The pharmacological activation of mesolimbic DA by drug reward persists throughout drug taking, in contrast to reward-evoked DA in response to natural rewards, such as food, which flexibly diminishes as that reward becomes expected. These chronically repeating drug-induced surges of DA have been proposed to act as aberrant DA RPE signals, leading to the overvaluation of cues and actions that precede drug procurement, biasing future behavior toward drug taking at the expense of other competing behavioral choices (Redish 2004).

DA RPEs initiated in the VTA-NAc circuit may propagate via their impact on accumbal MSNs to extended striatal domains, allowing DA RPE signals to promote plasticity in parallel corticostriatal circuits and thereby engage circuit-specific processes in the control of behavior (Belin et al. 2009, Everitt & Robbins 2016, Keiflin & Janak 2015). The chronic drug-induced overstimulation of DA neuron firing and DA release may distort this process (Keiflin & Janak 2015) and, along with other neurobiological changes reviewed below, underlie the transition to addictive behavior.

Key among these neurobiological changes are drug-sensitive plasticity mechanisms in the VTA that are permissive for striatal plasticity. When this plasticity is present in the VTA for a few days, potentiation of excitatory afferents also appears in the NAc (Mameli et al. 2009) and later in the DST through the recruitment of more dorsal and lateral corticostriatal loops. For example, exposure to cocaine potentiates D1R-MSN GABAergic inputs on midbrain GABAergic neurons, leading to long-term increases in tonic DA neuron firing (Bocklisch et al. 2013). The patterns of neuronal connectivity provide a means for this potentiation to facilitate the disinhibition of DA neurons not only in VTA but also in substantia nigra pars compacta (SNc), in effect hastening the normal propagation of RPEs from NAc to SNc–dorsal striatal circuits. This may provide a mechanism for the enhanced recruitment of more dorsal striatal circuits observed following chronic drug self-administration (Belin & Everitt 2008, Porrino et al. 2004). While details of this model require empirical testing, these and other data suggest that reward-relevant neural processing in the VTA-NAc pathway precedes, and may contribute to, the development of such processing in more dorsal striatal circuits, providing a route whereby excessive drug-induced DA can initiate transitions to compulsion.

MODELING COMPULSION IN RODENTS

The transition to addiction can be broken down into three steps (Piazza & Deroche-Gamonet 2013): (*a*) recreational drug use, (*b*) intensified-sustained-escalated drug use, and (*c*) loss of control of drug use and full addiction. Rats were assessed by (*a*) drug seeking once the drug was no longer available, (*b*) break points during progressive ratio schedules of reinforcement, and (*c*) persistence of self-administration despite punishment (contingent electric foot shock). Monitoring these three behavioral criteria, which are loosely modeled after *The Diagnostic and Statistical Manual of Mental Disorders* criteria, yields cocaine addiction in about 20% of rats (Deroche-Gamonet et al. 2004). Demonstrating compulsive self-administration of an addictive drug in rodents is challenging because of the long duration of the experiment (keeping the small catheters open over weeks is especially difficult in mice) and the fact that only a minority of animals eventually lose control, which requires very large sample sizes to yield statistically reliable findings in studies investigating the underlying neural mechanisms. Perseverance despite punishment may be the most discriminative marker, as unbiased clustering of several behavioral parameters during this task (e.g., delay pushing lever, velocity at which trials are performed, futile lever or inactive lever presses, seeking lever presses) shows the emergence of a bimodal distribution. Compulsion is thus operationally defined as the continued self-administration of a drug in the presence of an aversive stimulus, such as an electric shock or a strong air puff, or in the case of oral self-administration, the presentation of bitter quinine in the drug solution. Similar to humans, most animals will stop self-administration when facing such punishment.

Two extensions of this paradigm add face validity to the behavioral paradigm. First, it has been argued that offering an alternative reward, such as a sweet water solution, may deter the animal from self-administering an addictive drug such as cocaine or heroin (Lenoir et al. 2007, 2013). Indeed, when facing a choice between an intravenous drug injection and sweetened water delivered immediately, most animals, particularly in the early stages of self-administration, develop a preference for the nondrug alternative (Ahmed et al. 2013). Even after long-standing access and escalation, many animals choose sucrose over the drug. However, a recent analysis of the temporal pattern of self-administration concluded that cocaine represents a delayed reward compared to the immediate alternative (Canchy et al. 2020). Congruent with these findings, cocaine causes a slow-onset but long-lasting DA transient. These pharmacokinetic properties therefore explain the initial preference for an immediate reward but also the addiction liability, which will eventually shift the preference to the drug. Combining punishment after established drug self-administration with an alternative reward, a recent study also found a bimodal distribution, with about one-third of the rats self-administering cocaine compulsively (Degoulet et al. 2019).

Dopamine transporter (DAT): expressed on the cell membrane for the reuptake of the transmitter from the extracellular space

Second, it has been argued that compulsive drug seeking is more relevant for addiction than compulsive drug taking (Jonkman et al. 2012). Refining the self-administration paradigm by introducing a seeking–taking chain using two levers in the operant box allows for separate examination of these phases. The seeking lever needs to be pressed during a period of pseudorandom duration [a so-called random interval (RI), whereby the duration varies around a given mean, e.g., durations of 45, 60, and 75 s to yield a RI of 60s]. At the end of the RI, the first seeking lever press triggers the second lever extension that, when pressed, triggers the injection of the drug. To test for compulsion, the last seeking lever press triggers an aversive stimulus in about 30% of the trials.

Compulsion can also be studied in an addiction model using optogenetic dopamine neuron self-stimulation (oDASS) instead of drug self-administration (Pascoli et al. 2015, 2018). oDASS builds on the defining commonality of addictive drugs—that they drive positive reinforcement via enhanced mesoaccumbal DA levels. Thanks to the specificity of the manipulation and to the fact that about 50% of animals develop compulsion, oDASS facilitates mechanistic investigations. In brief, after injection of an adeno-associated viral vector containing the floxed, inverted version of enhanced channelrhodopsin-2 (ChR2) into the VTA of dopamine transporter (DAT)-Cre mice, the mice quickly learn how to self-stimulate in an operant box. Pairing a specific environment with the optogenetic stimulation of VTA DA neurons leads to an immediate place preference that persists for several days (Adamantidis et al. 2011, Tsai et al. 2009). In line with these early reports, strong reinforcement becomes apparent as mice readily maintain intake if the fixed ratio increases, and they are willing to press several hundred times in a progressive ratio schedule used to determine the break point for motivation. Just like with drug self-administration, oDASS can be tested with a risk of punishment such as an electric shock or air puff. Almost all mice slow down their self-stimulation rate once electric shocks are delivered, albeit with much individual variability. In fact, some mice stop responding, whereas others keep performing oDASS, taking only slightly more time or reducing the seeking lever presses (Harada et al. 2019). While the histogram for the oDASS rate is unimodal during the baseline sessions, it becomes bimodal by the end of a few punished sessions. A clustering method applied to the entire behavioral data set confirms the emergence of two groups of almost equal size: mice with a little decrease in oDASS rate during punished sessions (called perseverers) and mice with a strong decrease in oDASS (called renouncers) (**Figure 2**).

A variant to oDASS is optogenetic GABA neuron self-inhibition (oGABASI), whereby glutamic acid decarboxylase–Cre mice are infected with ArchT3.0 (Corre et al. 2018). The mice press a lever triggering an amber light stimulation, which reduces activity of the ArchT3.0-expressing GABA neurons in the VTA. This approach mimics the dopamine neuron disinhibition scenario of drugs such as opioids, cannabinoids, and benzodiazepines and allows the study of the positive reinforcement component in isolation. Given the specificity of the oDASS and oGABASI interventions on the mesolimbic system and the significantly larger yield of compulsive mice, mechanistic investigations within relevant circuits are greatly facilitated.

CIRCUITS OF NEGATIVE REINFORCEMENT

Addictive drugs, and opioids in particular, drive behavior through production of both appetitive states and aversive states (including hyperalgesia) (Corder et al. 2013, Koob 2020), and these

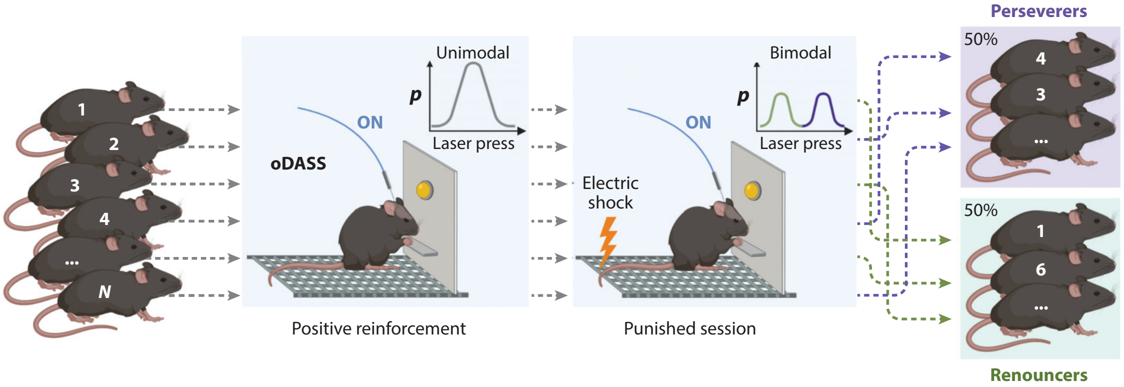

Figure 2

Stochastic transition toward compulsion. Acquisition of ventral tegmental area optogenetic dopamine neuron self-stimulation (oDASS) is unimodally distributed with only a little variance. Upon the introduction of an aversive stimulus (punishment), some animals renounce oDASS, while others continue even when having to endure the negative consequences. As a result, a bimodal distribution emerges. Given the variance, typically 50–100 animals have to be tested.

aversive states upon drug cessation may shape adaptive behavior by avoidance of withdrawal. The latter aversive component has been conceptualized as a so-called opponent process that builds up iteratively as the subject becomes dependent (Koob & Schulkin 2018, Solomon 1980). With opioids, the stereotypical withdrawal syndrome is particularly unpleasant, but withdrawal can also be observed, to varying degrees, with other drugs. For opioids, negative reinforcement depends on μ opioid receptors (μORs), as the genome-wide knockout mouse (Matthes et al. 1996) shows no withdrawal symptoms when challenged with naloxone after chronic morphine exposure. μORs expressed in the habenula have been implicated in naloxone-induced withdrawal symptoms (Boulos et al. 2020). Stress hormones such as the corticotropin-releasing factor (CRF) (Grieder et al. 2014, Park et al. 2015) and the hypothalamic-pituitary-adrenal axis more generally (Zhou et al. 2006) have also been implicated. Alternatively, the noradrenergic system was hypothesized to be involved, as the locus coeruleus (LC) becomes hyperactive during withdrawal. However, manipulations of LC activity failed to affect behavior (Christie et al. 1997). For other drugs such as cocaine, where a withdrawal syndrome is not readily observed, negative reinforcement may be reflected by a loss of hedonic experience to natural rewards (Creed et al. 2016) and contributes to motivation to resume cocaine intake.

Based on the hypothesis that circuits that mediate physiological aversion may also underlie negative reinforcement of addictive drugs (**Figure 3**), it is thought that several brain structures may contribute. For example, the medial habenula, which expresses a very high density of μORs, may also undergo adaptations causing dysphoria, perhaps via its projections to the interpeduncular nucleus or to the lateral habenula (LHb), an excitatory nucleus projecting to GABA neurons in the tail of the VTA [also called the rostromedial tegmentum (RMTg)], which then inhibit VTA DA neurons (Mechling et al. 2016). The paraventricular thalamus (PVT) and parts of the basolateral amygdala (BLA) that convey negative valence in a fear conditioning paradigm (Beyeler 2016) may also contribute. The amygdala is also involved in the observation that craving grows during the first couple of months of withdrawal, a phenomenon called incubation of craving (Grimm 2001).

The BLA to NAc projection seems to encode both rewarding and aversive signals, with the latter carried by cells in the BLA that express the cholecystokinin (CCK) marker (Shen et al. 2019). These CCK+ neurons project onto dopamine receptor 2 (D2R)-MSNs and aversion results from

Rostromedial tegmentum (RMTg): a nucleus adjacent to the ventral tegmental area made of γ-aminobutyric acid neurons that inhibit dopamine neurons

Incubation of craving: cocaine seeking, when triggered by reexposure to drug-associated cues, progressively increases over the first 2 months after withdrawal from self-administration of the drug

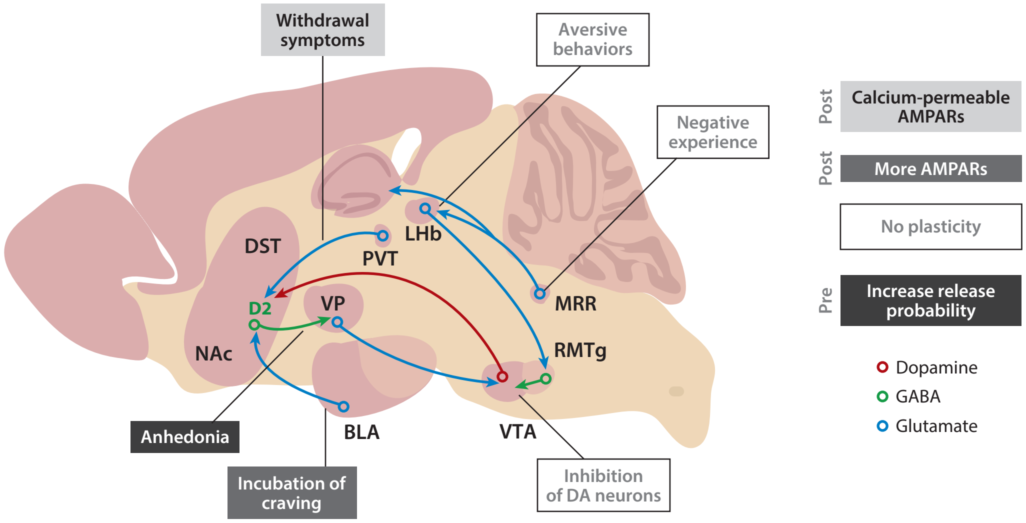

Figure 3

Circuits of negative reinforcement. The MRR constitutes a hub that, via the LHb, reaches the RMTg, where GABA neurons that eventually inhibit VTA DA neurons are stimulated. Other excitatory inputs converge from the BLA (mostly CCK-positive neurons) and the PVT onto D2R-MSNs of the NAc. Anhedonia has been linked to D2R-MSN projections to the VP, which undergo presynaptic depression upon cocaine withdrawal. Opioid withdrawal symptoms have been linked to plasticity at PVT to D2R-MSN synapses and incubation of craving to the potentiation of BLA afferents onto the same neurons. Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BLA, basolateral amygdala; CCK, cholecystokinin marker; D2R, dopamine receptor 2; DA, dopamine; DST, dorsal striatum; GABA, γ-aminobutyric acid; LHb, lateral habenula; MRR, median raphe region; MSN, medium spiny neuron; NAc, nucleus accumbens; PVT, periventricular thalamus; RMTg, rostral tegmentum; VP, ventral pallidum; VTA, ventral tegmental area. Figure adapted from Lüthi & Lüscher (2014).

the activation of terminals of these projections in the NAc. In addition, Ppp1r1b+ and Rspo2+ mark BLA neurons that are preferentially activated by reward-related or aversion-related stimuli, respectively, and Rspo2+ neurons do project to the NAc (Kim et al. 2016). An aversion circuit that converges onto D2R-MSNs is thus emerging, which may drive the negative reinforcement following chronic drug exposure. Indeed, in the case of PVT neurons projecting to NAc D2-MSNs, a causal relationship with certain opioid withdrawal symptoms has been established (Zhu et al. 2016).

The BLA also projects to the central nucleus of the amygdala (CeA), mediating both appetitive and aversive valence, the latter through Rspo2+ neurons (Kim et al. 2016). CeA in turn sends GABAergic projections to the LH, the VTA, the pedunculopontine nucleus, and the periaqueductal gray (PAG). Pharmacological blockade of CRF1 receptors in the CeA blocks the aversive nature of opioid withdrawal (as measured by the effect on withdrawal-induced conditioned place aversion) and dependence-induced hyperalgesia (Heinrichs et al. 1995, Koob 2020, Park et al. 2014).

Recent evidence suggests that a population of excitatory, vesicular glutamate transporter 2 (vGluT2)-expressing neurons in the mouse median raphe region orchestrates the activity in downstream aversion centers, such as the LHb (Szőnyi et al. 2019). During cocaine withdrawal, the time of immobility is longer in the forced swim test, a test for depressive-like behavior. This behavioral state has been linked to a synaptic potentiation of the LHb to the RMTg projection by insertion of the GluA1subunit of AMPA receptors (AMPARs) (Meye et al. 2015). Taking advantage of this mechanistic insight, a selective inhibition of membrane delivery of GluA1 also blocks depressive-like behavior during withdrawal, suggesting a link of causality.

AMPA receptor (AMPAR): ionotropic glutamate receptor defined by its selectivity for α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

Additional transmitter systems may also play a role. For example, dynorphin, which is produced by D1R-MSNs, is upregulated during withdrawal, inducing dysphoria via the activation of kappa opioid receptors (κORs) that are located on DA terminals (Muschamp & Carlezon 2013). Dynorphin causes presynaptic inhibition of DA release in the NAc and PFC through G_{io} activation and βγ signaling. κORs are expressed on the cell bodies of D1R- and D2R-MSNs as well as at the terminals of glutamatergic projections from the BLA, which could also contribute to negative reinforcement. Moreover, as mentioned above, DA neurons themselves may also drive negative reinforcement, since a subset is activated by aversive stimuli (whereas most DA neurons are typically inhibited by aversive stimuli). Aversive DA neurons may project to the medial prefrontal cortex (mPFC) (Lammel et al. 2012) and to the tail of the DST (Menegas et al. 2018). The acute effects of addictive drugs on these neuronal populations and the adaptive changes that occur with chronic exposure, however, have not been investigated.

Regardless of how drugs recruit so-called aversion circuits, a crucial question for a better understanding of the contribution of negative reinforcement to the transition to compulsion is their convergence with circuits of positive reinforcement. Since circuits of positive and negative reinforcement intersect in the NAc, this hub probably plays an initial role in the progression to compulsion. Accumbal direct-pathway D1R-MSNs project to the midbrain (preferentially onto GABA neurons) (Bocklisch et al. 2013) and also to the ventral pallidum (VP), while D2R-MSNs of the indirect-pathway (also labeled by adenosine A2 receptors) first exclusively project to the VP and only then to the midbrain (Creed et al. 2016). After chronic exposure to cocaine, D1R-MSN projections become potentiated while D2R-MSNs that were depressed mediate sensitization and impair processing of natural reward, respectively. The VP thus emerges as a potential hub for the integration of positive and negative reinforcement (Wulff et al. 2019). The two neural populations of MSNs thus interact again in the midbrain. Therefore, the initial adaptations in the NAc may be permissive for later-stage changes in the midbrain, where the indirect pathway may interfere with the spiraling connectivity of the direct pathway. Through the disinhibition of more and more lateral VTA DA neurons, these D1R-MSNs also recruit more dorsal parts of the striatum (Haber et al. 2000; for a review, see Ikemoto et al. 2015), eventually relaying the information from the mesolimbic to the nigrostriatal DA projection.

CIRCUITS OF COMPULSION

A leading hypothesis posits that corticostriatal projections control the transition to compulsion (Everitt & Robbins 2016, Lüscher et al. 2020). While some studies have claimed a hypofunction of the prefrontal cortex, and of the mPFC in particular (Chen et al. 2013), others found a hyperactivity of the orbitofrontal cortex (OFC) to DST projection in compulsive mice (Pascoli et al. 2015). An appealing hypothesis is thus the progression of top-down control to more and more lateral parts of the prefrontal cortex, yet the sequence of events is only starting to emerge. Activity changes in the mPFC may thus precede alterations in the OFC. Several projection streams constitute the cortical top-down control of the striatum originating in the mPFC and the OFC (Harada et al. 2019).

The mPFC is composed of the pre- and infralimbic parts that map to Brodmann areas 32 (PL) and 25 (IL), respectively, to the anterior circulate cortex (ACC, area 24), and to the medial precentral area (areas 9 and 10) (Heidbreder & Groenewegen 2003). In rodents, only areas 9 and 10 are granular; the rest is agranular, thus lacking layer IV. Therefore, most of the inputs arrive in layers II and III, and the outputs originate in layers V and VI. Glutamatergic projections target many cortical and subcortical areas, particularly the NAc core (mainly from PL) and shell (mainly from IL) (Britt et al. 2012, Suska et al. 2013) as well as the medial dorsal striatum.

The OFC comprises the anterior and ventral parts of the PFC and is subdivided into a medial and lateral region. In humans, the OFC has three major cytoarchitectonic regions: the anterior region (area 11), the posterior region (area 13), and the medial region (area 14). It also includes the ventral portions of areas 10 and 47/12 (Wallis 2007). Four sulci divide the surface of the OFC into five gyri limited by the insular cortex, located caudally. Areas 11, 10, and 47/12 are made of six layers and are considered granular cortex, while areas 13 and 14 range from agranular to dysgranular (Öngür et al. 2003). In nonhuman primates, the OFC is very similar to the human OFC (Ongür & Price 2000), which allows for cross-species translation of anatomical connectivity. In rodents, the OFC is agranular and divided into four main regions: the medial orbital region, the lateral orbital region, the ventro-orbital region, and the dorsolateral orbital region (Van De Werd et al. 2010, Wallis 2012). The major inputs to the OFC are the medial dorsal thalamus and the sensory cortices (Chen et al. 2014, Mátyás et al. 2014, Ongür & Price 2000). The OFC and the medial dorsal thalamus [particularly the submedius thalamic nucleus (SUB) (Yoshida et al. 1992)] are reciprocally connected, with all the sensory modalities converging in the OFC. In rodents, the OFC also has reciprocal connections to the BLA. The major outputs of the OFC are to the DST as well as to the hypothalamus and PAG.

As stated above, outputs from the mPFC thus reach the ventral parts of the striatum, while the OFC preferentially connects to the DST. This is of interest in the context of the spiraling anatomical midbrain-striatal connectivity (Haber et al. 2000). In fact, DA neurons from the medial VTA project to the medial NAc shell, from which spiny projection neurons send axons off to the midbrain. Their primary targets are GABA interneurons, which synapse onto DA neurons in the lateral VTA. These cells project to the core and the lateral shell of the NAc. The repetition of this disinhibitory motive leads to the recruitment of more and more lateral DA neurons, eventually reaching the SNc in the process, giving off ascending projections to more and more lateral parts of the DST. Top-down cortical control by the mPFC thus touches the early loops of the spiral, while the OFC interferes with downstream loops. Following this logic, the ACC and the motor cortex control the most dorsolateral parts of the DST.

CORTICAL CONTROL OF DECISION-MAKING

Based on lesion experiments, the mPFC has been implicated in attention control, response inhibition, planning, and decision-making (Balleine & Dickinson 1998, Dalley et al. 2004, Euston et al. 2012, Miller & Cohen 2001) as well as in working memory, storing information for seconds to minutes, which is necessary when carrying out a complex task (Baddeley 1992). Human imaging studies also implicate the mPFC in pain processing (Ong et al. 2019). Noxious stimuli activate the mPFC, particularly regions that connect to the PAG, a hub in the pain pathway (Peyron 2014). In rodents, action control depends on the mPFC (Hardung et al. 2017). In a task where the rat needs to press a lever in a precisely timed fashion to obtain a reward, PL activity decreases prior to premature responses, while artificial inhibition promotes such responses. IL has the converse effect by reducing premature action.

Clues for OFC function come from patients with traumatic or ischemic damage, who show impairments of behavioral flexibility, decision-making, and goal-directed behavior (Stalnaker et al. 2015, Wallis 2007). The striking clinical picture, typified by the famous neurological patient Phineas Gauge (Macmillan 2000), has motivated many studies in humans, nonhuman primates, and rodents (Wallis 2012). Key functions that have been attributed to the OFC across species include encoding relative reward value and updating prior reward learning (Gremel & Costa 2013a). Reversal learning tasks allow for the investigation of these functions (Izquierdo & Jentsch 2012). In brief, the subject learns an action–outcome association over multiple pairings, such as pressing one of two levers for a sucrose reward. After the discrimination has been made between the two levers, the task reverses, and the subject must now press the other lever to earn the reward. This task requires the subject to stop performing the behavior that had previously proven effective and instead start performing the behavior that had previously proven useless. Behavioral flexibility and updating prior learning are key.

The functions of the OFC are therefore distinct from the adjacent mPFC, which lacks the value-updating function of action outcomes (Simon et al. 2015, Sul et al. 2010). Although neurons in the mPFC and in the OFC respond to action–outcome reward histories (Dalton et al. 2016), the former do not encode the reward-prediction error information that is essential to update expectations (but see Stalnaker et al. 2015). Recent evidence also indicates that neurons that project from the mPFC to the NAc are activated by aversive stimuli, and they control restraint of reward seeking when associated with a punishment (Kim et al. 2017). However, this observation may also reflect the established role of the mPFC in modulating pain perception (Bräscher et al. 2016, Seifert et al. 2009). Another difference is that OFC neurons respond to time costs and changes in the magnitude of the outcome, while the mPFC neurons are more responsive to the effort requirements of the task (Simon et al. 2015, Wallis 2007). It has also been shown that the OFC is important for interpreting the affective value of stimuli, while the mPFC is more important for determining which stimuli are relevant to the task (Bissonette et al. 2008). Taken together, the OFC seems to play the critical role in integrating new information about the values of outcomes over time, which may shape compulsive behavior in addiction, as discussed below.

Within the OFC, the functions of the medial and lateral regions are distinct for value updating and reversal learning. This was demonstrated with reward devaluation, a task related to reversal learning. When mice are trained on a random ratio schedule to press a lever for a food reward, they develop goal-directed behavior; when mice are trained on a RI schedule, they develop habitual behavior (Gremel & Costa 2013b). This can be revealed by giving the animal ad libitum access to the reward. An animal with a goal-directed behavior will stop pressing the lever for the now devalued reward, while a habitual animal will continue pressing the lever. This task is related to the reversal learning task because the animal must use the new information related to the value of the reward rather than new information related to the task itself. In this task, the lateral OFC is necessary for facilitating goal-directed actions. Chemogenetic inhibition of the lateral OFC decreased the effect of reward devaluation in mice trained on a random ratio schedule, resulting in more habitual behavior of mice initially showing goal-directed behavior, while it had no effect on mice that were already exhibiting habitual behavior (Gremel & Costa 2013a). Conversely, optogenetic stimulation enhanced the effect of reward devaluation in mice that had been trained on a RI schedule, resulting in more goal-directed behavior. By contrast, the medial OFC appears to be involved in aggregating relevant information to evaluate outcomes. With enhanced medial OFC activity, the new reward value is more effectively integrated. The medial OFC has also been shown to be important for integrating associative information that might be ambiguous (Bradfield et al. 2015). The SUB to lateral OFC projection has also been implicated in behavioral flexibility (Alcaraz et al. 2015). Taken together, this suggests that shifting from goal-directed action to compulsive behavior depends on changes in the lateral OFC, while the medial OFC controls the integration of relevant information and the updating of the value of rewards or actions.

ORBITOFRONTAL CORTEX IN COMPULSION

Given the physiological function of the OFC, its involvement in compulsion is not surprising and is supported by experimental evidence from human imaging studies as well as rodent behavior. For example, positron emission tomography imaging in cocaine addicts reveals a positive correlation

NMDA receptor: ionotropic glutamate receptor defined by its selectivity for *N*-methyl-D-aspartate and made of an obligatory GluN1 subunit that assembles with GluN2 or GluN3

between craving and OFC activity, and the projection to the NAc has been implicated in the compulsive component of consummatory behavior (Volkow et al. 2005). Several studies demonstrate altered OFC function after chronic drug exposure: Manipulation of OFC activity may restore the insight lost after cocaine self-administration and affect decision-making (Lucantonio et al. 2014). This may have to do with the reset of an inability to integrate information appropriately to predict reward values driven by pathological OFC activity (Lucantonio et al. 2015, Schoenbaum et al. 2016).

The OFC also emerges in unbiased c-Fos screening following compulsive cocaine self-administration or oDASS (Pascoli et al. 2015). When naïve animals are yoked together with compulsive ones, controlling for the difference in the number of aversive stimuli received (compulsive mice experience more shocks or air puffs), a positive correlation between the number of shocks and the c-Fos count emerges in the mPFC but not in the OFC, suggesting that the latter codes for compulsion independent of pain perception. Enhanced OFC activity can also be observed with electrophysiology and calcium imaging. In local field potential recordings in rats, the amplitude of theta oscillations is associated with subjective value and cocaine preference (Guillem & Ahmed 2018). Single-unit recordings then suggest the existence of specific neuronal assemblies whereby OFC phase-locked neurons fire on opposite phases of the theta oscillation during cocaine administration as well as during an alternate reward administration (Guillem & Ahmed 2020). In mice, the overall calcium signal increases briefly before the animal presses a lever inducing punishment. Ex vivo analysis of the projection to the DST, one of the most prominent output streams, indicates that this enhanced activity is associated with a potentiation of glutamatergic synaptic transmission onto MSNs, in both D1R- and D2R-SPNs. This finding is surprising in light of the rules for plasticity induction that have been established in brain slices of the DST (Shen et al. 2008). These rules also apply to the ventral striatum to some extent (Pascoli et al. 2014) and are rooted in the fact that D1Rs enhance while D2Rs decrease cyclic AMP levels. Coactivation of the D1Rs and NMDA receptors triggers the ERK/MapK pathway (Girault 2012), eventually leading to the insertion of additional AMPARs. Stimulation protocols that typically induce long-term depression (LTD) work in D1R-MSNs only if DA signaling is blocked (Creed et al. 2015). Conversely, D2Rs oppose potentiation of afferent glutamate transmission, while a dip in DA levels opens a long-term potentiation window for glutamate afferents onto D2R-MSNs (Iino et al. 2020). Artificially overriding these rules (e.g., by pairing LTD induction protocol with the pharmacological blockade of D1Rs) efficiently depotentiates OFC to DST synapses in compulsive mice and reduces oDASS perseverance in spite of aversive stimuli. Conversely, artificial potentiation in noncompulsive mice induces compulsion, fully establishing causality between the synaptic strength of glutamate transmission and compulsive behavior (Pascoli et al. 2018).

How the difference between compulsive and noncompulsive, renouncing animals arises remains unknown. An appealing possibility is that that OFC-DST potentiation is in fact induced during early cocaine exposure in all animals, but once punishment sets in, normal transmission is restored in the renouncing individuals. In an unbiased analysis of more than 100,000 synapses along with electrophysiological assays using optogenetics to stimulate activated versus nonactivated inputs, stronger synapses between coactivated cortical pyramidal neurons and neurons in the DST in all mice (Wall et al. 2019) were revealed at a stage where compulsion had not yet emerged.

MODULATION OF TRANSITION TO COMPULSION

The transition to compulsive drug seeking and drug use is ultimately the result of the interplay between positive and negative reinforcement (**Figure 4**). This process is modulated by several

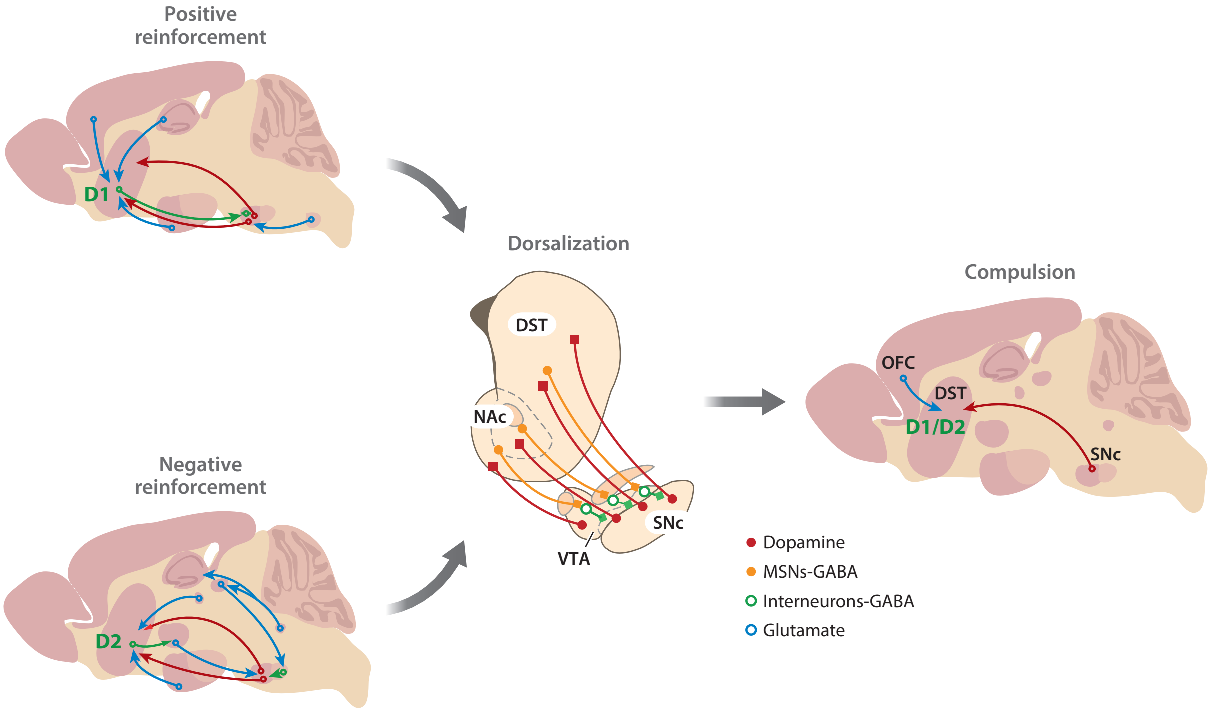

Figure 4

Modular assembly of a consolidated circuit model for addiction. Positive and negative reinforcement add up to drive the dorsalization. Through the spiraling, back projection of MSNs (directly to the midbrain in the case of D1R-MSNs and indirectly via the ventral pallidum for D2Rs), OFC to dorsal striatum circuits are recruited. Compulsion is then expressed by synaptic potentiation onto both D1R- and D2R-MSNs in vulnerable individuals. Abbreviations: D1R, dopamine receptor 1; D2R, dopamine receptor 2; DST, dorsal striatum; GABA, γ-aminobutyric acid; IN, interneuron; MSN, medium spiny neuron; NAc, nucleus accumbens; OFC, orbitofrontal cortex; SNc, substantia nigra pars compacta; VTA, ventral tegmental area. Figure adapted from Lüthi & Lüscher (2014).

factors. In rodents, the schedule of drug availability has a major impact on the transition to addiction. Extended heroin access, for example, considerably increases the choice of heroin at the expense of food rewards (Lenoir et al. 2013). Long access versus short access to cocaine is also a determinant for resistance to punishment (Pelloux et al. 2007). In addition, withdrawal from heroin increases the choice of heroin in nonhuman primates, even at low doses (Negus 2006, Negus & Rice 2009). Thus, repetitive withdrawal from opioids may favor the transition to addiction.

Environmental factors may contribute to the transition to addiction, as it matters whether the animal is in the home cage for drug consumption (Caprioli et al. 2009). Interestingly, the effect is the opposite for opioids and psychostimulants: Animals that have access to the opioid in their home cage (in fact, the experiment involved 23-h access in the operant box, which means that the operant box is considered as the home cage) show higher consumption of heroin than controls, while the converse is observed for cocaine.

Resistance to punishment: a behavioral assay in which a mild electric shock or an air puff is delivered when an animal self-administers an addictive drug to assess its motivational value

Serotonin may play a crucial role in the transition to compulsion by exerting bidirectional modulation. Depletion of serotonin in the forebrain can increase the fraction of individuals who become addicted to cocaine, while serotonin reuptake inhibitors reduce compulsive seeking (Pelloux et al. 2012). For cocaine, the observed transition to compulsion in about 20% of individuals may thus be the result of two opposing forces. DAT blockade drives the transition by maximizing positive reinforcement, while serotonin transporter blockade prevents this transition. In other words, the nonspecific pharmacological profile of cocaine may explain the relatively low transition rate, and selective DAT inhibitors are potentially more addictive. The specific DAT-Cre inhibitor GBR 12909 is indeed self-administered in rats in a way similar to cocaine (Roberts 1993), but transition to compulsion with this compound has not been tested to date. The cellular mechanism underlying the modulatory effect of serotonin remains elusive, but a modulatory role of 5-hydroxytryptamine on striatal synaptic plasticity (Dölen et al. 2013) seems to be an appealing hypothesis.

Cholinergic interneurons in the NAc may also modulate the transition to compulsion. First, acetylcholine released from these cells potentiates DA release by mesolimbic afferents (Di Chiara & Imperato 1988, Lüscher & Ungless 2006, Wise & Robble 2020), and it could thus promote synaptic adaptations underlying drug adaptive behavior and, eventually, compulsion. The activity of cholinergic interneurons is further regulated by D2Rs expressed on their somas and dendrites. Unlike MSNs, cholinergic interneurons express G protein–coupled inwardly-rectifying potassium channels, the D2R effectors responsible for dampening their activity. A recent study, in which D2Rs were overexpressed in cholinergic interneurons, argues for a causal link to resistance to punishment in a cocaine self-administration paradigm (Lee et al. 2020).

Stress can amplify drug craving and the transition to compulsion. Prepubertal stress by early separation from the mother, for example, enhances the fraction of compulsive animals (Baarendse et al. 2013). A well-investigated neural correlate of stressors is the activity in the hypothalamic pituitary axis, which can predict relapse (Sinha et al. 2006). Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. CRF is an additional neuromodulator that has been implicated in mediating consequences of withdrawal. For example, CRF in the CeA may underlie anxiety experienced during cocaine withdrawal (Zhou et al. 2004). Increased CRH messenger RNA levels are found in the amygdala during short-term withdrawal from chronic cocaine binging (Zhou et al. 2003) and CRF-R1 antagonists attenuate stress-induced reinstatement of heroin (and cocaine) seeking in rats (Shaham et al. 1998, 2000). A subpopulation of amygdala neurons in the CeA are activated by alcohol withdrawal and are largely CRF positive (de Guglielmo et al. 2019). Suppression of these CRF-positive neurons in the CeA reduces escalation of alcohol intake and alcohol withdrawal symptoms.

Last but not least, sex is also discussed as a determinant of the transition to addiction (Kerstetter et al. 2013), as female rats seem to be more vulnerable to cocaine addiction (Calipari et al. 2017). In the oDASS model, however, this difference was not observed (oDASS leads to compulsion in about 50% of individuals, regardless of sex), suggesting the involvement of drug targets other than DA reuptake inhibition.

EPIGENETICS OF INDIVIDUAL VULNERABILITY

It is likely that one or several factors listed above determine the preexisting vulnerability of an individual. Interestingly, in genetically homogeneous populations, such as the C57BL/6J mouse line, the proportion of compulsive individuals is very similar to the fraction observed in humans. Behavioral differences between C57BL/6 substrains exist, including addiction-relevant traits [e.g., C57BL/6J mice seem to have a stronger preference for alcohol than do C57BL/6N mice (Blum et al. 1982, Hwa et al. 2011)]. However, to the best of our knowledge, no drug-adaptive behavior has been linked to polymorphic variance within the C57BL/6J strain. As a proof of principle for individuality emerging in identical C57BL/6J mice, close monitoring of exploratory activity revealed increasing differences with age (Freund et al. 2013). A bimodal distribution for compulsion can thus also emerge from a population of individuals who are genetically identical. Therefore, three scenarios seem plausible to account for behavioral individuality in genetically identical mice: (*a*) remaining minimal residual segregation, as perfect inbreeding is impossible; (*b*) stochastic gene expression; and (*c*) epigenetic drift caused by small differences in the environment. The life experience of a mouse may thus lead to the expression of several genes in neurons that are part of the positive and negative reinforcement circuits, altering the function of these neurons and eventually modulating the transition to compulsion.

Defining behavioral endophenotypes that predict individual vulnerability (Belin et al. 2016) is of great interest in the context of a genetically homogeneous population. For example, impulsivity, i.e., excessive premature responding (Belin et al. 2008), is one trait that has been linked to compulsive drug taking in both humans and animal models (Egervari et al. 2018, Elam et al. 2016, Henges & Marczinski 2012). Although high impulsivity in rodents can predict compulsive cocaine seeking (Sanchez-Roige et al. 2014), the causal relationship remains elusive. Furthermore, high impulsivity in rodents does not predict escalation of heroin self-administration (McNamara et al. 2010), suggesting that impulsivity may not predict vulnerability to addiction for drugs where negative reinforcement is prominent. Therefore, identifying endophenotypes rooted in the circuits targeted by all addictive drugs may lead to more stringent predictions of individual vulnerability to addiction.

While several studies have examined the effects of cocaine on epigenetic regulation (Nestler & Lüscher 2019), only a few studies have investigated the possibility that epigenetic mechanisms may underlie individual vulnerability for addiction. Based on the response to a natural reward, the quantification of motivation, and relapse, some rats were classified as vulnerable for compulsive drug taking. In this subpopulation, higher levels of some microRNAs were found in the striatum compared to those in the control group (Quinn et al. 2015). There may also be a correlation between stress and addiction vulnerability along with the adaptation of epigenetic markers (Cadet 2016). The hypothesis, although it has not been directly tested, argues that stress and addictive drugs drive similar epigenetic changes, which is why epigenetic markers of stress might also underlie vulnerability to addiction. Another line of research examines the heritability of epigenetic changes (Morrow & Flagel 2016, Vassoler et al. 2013). Animals that are exposed to various drugs can pass on epigenetic markers associated with drug exposure, such as DNA methylation of relevant promoters, to their offspring. Interestingly, cocaine-exposed animals pass on a histone acetylation pattern of the brain-derived neurotrophic factor promoter to their offspring that may be protective, as it confers resistance to cocaine reinforcement. However, these heritable, drug-related epigenetic changes likely do not explain individual differences in vulnerability to compulsive drug taking in lab animals whose parents have never experienced a drug. Understanding the epigenetic modulation of gene expression that distinguishes the vulnerable from the resilient in broad contexts rather than specific conditions of particular stressors or parental drug exposure would be invaluable in predicting who will be vulnerable to a variety of compulsive behaviors.

IMPLICATIONS FOR THERAPY

Despite initial hopes for rapid translation, to date, new therapies for addiction based on the proposed circuit model are only just emerging. Since in the VTA and NAc, metabotropic glutamate receptors (mGluRs) control the removal of calcium-permeable AMPARs (Bellone & Lüscher 2006, McCutcheon et al. 2011), agonists or positive allosteric modulators of these receptors may restore normal transmission and thus treat drug-adaptive behavior. While it may reduce the motivation for drug use, there is no evidence that this approach will have an impact on already established compulsion.

Since optogenetic stimulation protocols can reverse drug-adaptive behavior, this approach may have translational implications with the goal of allowing an addict to regain control. Optogenetic interventions in humans are still many years off, but, in the meantime, deep brain stimulation

(DBS) and transcranial magnetic stimulation (TMS) can be explored for rational approaches, even though electrical and magnetic stimulation remain nonspecific, and the sought-after effects may be masked by the activation of other neural structures and projections. The design of novel DBS protocols may take advantage of successful optogenetic manipulations in preclinical disease models that are emulated with DBS. Such optogenetically inspired DBS approaches may be the hic et nunc translation of optogenetics.

A handful of studies provide proof of principle for the use of DBS in addiction approach. For example, low-frequency DBS stimulation in combination with a D1R antagonist reverses locomotor sensitization to cocaine as efficiently as optogenetic depotentiation (Creed et al. 2015). Both of these approaches rely on mGluR-LTD. In the case of optogenetic depotentiation, mGluR1s are selectively activated, while D1R antagonists are needed for electrical stimulation (SCH 23390 or SCH 31166), since there is also DA release. Such an optogenetically inspired DBS protocol contrasts with classical DBS protocols in three points: It (*a*) uses intermittent, low frequency stimulation; (*b*) uses a pharmacological adjuvant; and (*c*) creates a lasting effect.

Given the consolidated model, other circuit nodes may be of interest, particularly the cortical areas, which may even be accessible to TMS, as suggested by a pilot study (Terraneo et al. 2015).

A recent study in rodents indicates that DBS, at its typical frequency above 100 Hz, of the OFC curbed morphine preference, facilitated its extinction, and blocked drug priming–induced reinstatement of morphine seeking (Fakhrieh-Asl et al. 2020). While the underlying mechanism remains to be investigated, it is tempting to speculate that a general inhibition of the OFC may make the decision to choose the drug less appealing. DBS of the subthalamic nucleus may also reverse escalated cocaine use (Pelloux & Baunez 2013).

CONCLUSIONS AND PERSPECTIVES: A GAIN-OF-FUNCTION DISEASE

In summary, we have reviewed studies aiming to elucidate the circuit mechanisms underlying the observation that only a minority of recreational drug users eventually fulfill the diagnostic criteria for addiction (Kessler et al. 2004, Wagner & Anthony 2002). Although a general theory for addiction (Piazza & Deroche-Gamonet 2014) is still far off, there is reason to be optimistic, as there have been substantial conceptual advances. The common belief that addiction is a neurodegenerative disease has been superseded by the consensus that drugs excessively stimulate the mesolimbic reward system, creating strong positive reinforcement, which, when paired with negative reinforcement during withdrawal, alters neural decision-making circuits, such that some individuals become compulsive. While several modulating factors have been identified, the molecular basis of individual vulnerability is still poorly understood, but it may involve epigenetic remodeling of the neurons constituting circuits of compulsion, such as the projection from the OFC to the DST. Future therapies will take advantage of such a circuit model to prevent or treat addiction.

FUTURE ISSUES

1. How does compulsion emerge? There is some evidence for which circuits control a compulsion once it has manifested. However, we know little about when these changes emerge and how individual differences come about. Is there a predisposition that is deterministic, or is there a truly stochastic process that is triggered once punishment sets in?

2. What is the driving force for the recruitment of dorsal circuits? Circuits of compulsion are located in the dorsal striatum, which receives its primary dopamine (DA) input from the substantia nigra pars compacta and which eludes the initial pharmacological increase of DA levels in response to addictive drugs. It is therefore likely that the spiraling circuit motif connects the ventral and dorsal parts of the striatum.
3. Which circuit element is best suited for a therapeutic intervention? The ideal site of intervention will depend on accessibility as well as its effect on addiction behavior. Deep brain stimulation works best when targeting small nuclei with a dense neural population (e.g., subthalamic nucleus for Parkinson's disease), while magnetic stimulation may be more suitable for cortical regions. Regardless, clinical trials will be challenging, as clinical cohorts are difficult to constitute given the nature of the disease.

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