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CONSOLIDATING THE CIRCUIT MODEL FOR ADDICTION

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■ **Abstract** Addiction is a disease characterized by compulsive drug seeking and consumption that 20-30% of users develop. 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, including compulsive drug-seeking and taking. 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 is built 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. Much recent data converges on a gain-of-function explanation for circuit remodeling, revealing blue prints for novel addiction therapies.

Keywords, dopamine, compulsion, negative reinforcement,

INTRODUCTION

The compulsive nature of drug-seeking and consumption defines drug addiction (American Society of Addiction Medicine 2011). Addicts lose control over their consumption, which continues unabated despite major negative consequences. These may include economic strain, but also social withdrawal, with betrayal in the family 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. This will however 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 will-power and support, addicts may withdraw from consumption, which is very painful, particularly with opioids. The withdrawal syndrome defines the dependence to the drug and its avoidance is referred to as negative reinforcement.

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-dependent reinforcement and place preference to cocaine is observed from drosophilae to honeybees (Søvik et al., 2014) and rodents. Cocaine also leads to chemosensory cue conditioning in C. elegant (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, typically using a behavioral pharmacology approach. Over the last tow decades, the focus has shifted to mice, because of the ease of genome editing. Positive reinforcement as well as initial drug adaptive behavior, such as locomotor sensitization, conditioned place preference or 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 (credriverlines.org), cell type-specific observations and manipulations have enabled an circuit interrogation with unprecedented precision.

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 dopamine (DA) levels (Di Chiara & Imperato 1988; Lüscher & Ungless 2006). We argued that the modulatory role of dopamine on glutamate transmission evokes forms of drug-adaptive plasticity in many synapses. This is a staged process that starts in the 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 had 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 D1R-MSNs in the NAc abolishes cue-associated seeking behavior (Pascoli et al. 2012).

Even though the initial model offers mechanistic insight into how drugs usurp circuits of reward and motivation to change behavior, it has several shortcomings. First, it is 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 2019). The contribution of such negative reinforcement is particularly visible for opioids, 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 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).

Here, we will briefly review the initial version of the model and then address the three limitations listed above: 1. Contribution of negative reinforcement, 2. Stochastic transition to compulsion and 3. Modulation by additional transmitter systems. We will also review the impact on therapeutic strategies, which to date - alas - remain still limited. While much progress has been achieved, we will 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 tested increased dopamine levels in the NAc (but only minimally in the dorsal striatum) 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 dopamine 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 dopamine neurons previously transfected with an optogenetic actuator is strongly reinforcing (Witten et al. 2011), (Pascoli et al. 2015), and so is the self-inhibition of VTA 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 that mediates error-driven learning, as described in temporal difference reinforcement learning models (Schultz et al. 1997). This role of dopamine as a teaching signal provides a framework in which to understand how the strong, sustained impact of abused drugs on mesolimbic dopamine may set in motion the neurobiological changes underlying the transition to addictive behavior (Redish 2004) Keiflin and Janak, 2015). The pharmacological activation of mesolimbic DA by drug reward persists throughout drug taking, in contrast to reward-evoked DA in response to natural rewards, like food, that 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 over-valuation of the cues and actions that precede drug procurement, biasing future behavior towards 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 medium spiny neurons 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) (Keiflin & Janak 2015)(Everitt & Robbins 2016a). 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, first in the NAc (Mameli et al. 2009) that may then facilitate the recruitment of more dorsal and lateral corticostriatal circuits. For example, exposure to cocaine potentiates D1 MSN GABAergic inputs on midbrain GABAergic neurons leading to long term

increases in DA neuron firing (Bocklisch et al 2013). The patterns of neuronal connectivity provide a means for this potentiation to facilitate disinhibition of DA neurons not only in VTA but also in 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 (Porrino et al. 2004)(Belin & Everitt 2008). 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

Transition to addiction can be broken down into three steps (Piazza & Deroche-Gamonet 2013): i. *Recreational drug use,* ii. *Intensified-Sustained-Escalated drug use,* and iii. *Loss of control of drug use and full addiction*. Rats were assessed by (i) drug-seeking once the drug was no longer available, (ii) breakpoints during progressive ratio schedules of reinforcement, and (iii) persistence of self-administration despite punishment (contingent electric foot-shock). Monitoring three behavioral criteria loosely models after the DSM criteria and it yields about 20% cocaine "addicted" rats (Deroche-Gamonet et al. 2004). The demonstration of compulsive drug 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 not all animals eventually lose control (requirement for very large sample sizes). Perseverance despite punishment may be the most discriminative, 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 in the presence of an aversive stimulus, such as an electric shock or a strong air puff, as well as opposing oral SA with the presentation of a bitter quinine solution. Like in humans, most individuals 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 with cocaine or heroin (Lenoir et al. 2007, 2013). Indeed, most animals, particularly in the early stages of self-administration, when facing a choice between a drug i.v. injection and sweetened water delivered immediately, develop a preference for the non-drug 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 SA with an alternative reward, a recent study (Degoulet et al. 2018) also found a bimodal distribution, with about 1/3 of the rats self-administering cocaine compulsively.

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 accounts for this. In brief, in a two-lever operand box, the "seeking lever" needs to be pressed during a period of pseudorandom duration (so called random interval, RI, whereby the duration varies around a given mean, e.g. duration of 45s, 60s and 75s 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 will trigger an aversive stimulus in about 30% of the trials.

Compulsion can also be studied in an addiction model using optogenetic DA neurons self-stimulation (oDASS) instead of drug SA (Pascoli et al. 2015, 2018). oDASS builds on the defining commonality of addictive drugs that they drive positive reinforcement via enhanced meso-accumbal 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 AAV containing the floxed, inverted version of enhanced ChR2 into the VTA of DAT-Cre mice, the mice quickly learn how to self-stimulate in an operant box. Pairing a specific environment with 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 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, an electric shock or an 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 the optogenetic GABA neuron self-inhibition (oGABASI), whereby GAD-cre mice are infected with ArchT3.0 (Corre et al. 2018).The mice press a lever triggering an amber light stimulation. This mimics the 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 are greatly facilitated.

CIRCUITS OF NEGATIVE REINFORCEMENT

Addictive drugs, opioids in particular, drive both appetitive, reinforcing and negative, aversive behaviors (including hyperalgesia, Corder et al., 2013) that may shape adaptive behavior by avoidance of withdrawal. The latter has been conceptualized as an "opponent process" that builds up while the subject becomes dependent (Koob & Schulkin 2018; Solomon 1980). With opioids, the stereotypical withdrawal syndrome is particularly unpleasant, but this can also be observed, to a lesser extent, with other drugs. For opioids, negative reinforcement also depends on 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. 2019). Stress hormones such as the corticoid-releasing factor (CRF, (Grieder et al. 2014) and the hypothalamic-pituitary-adrenal axis (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 withdrawal is not readily observed, negative reinforcement may be reflected by a loss of hedonic experiences to natural rewards (Creed et al. 2016).

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, maybe *via* its projections to the interpeduncular nucleus or to the lateral habenula, an excitatory nucleus projecting to GABA neurons in the tail of the VTA (also called 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. Indeed, aversion results from the activation of terminals of these projections in the NAc. The BLA to NAc projection codes for both rewarding and aversive stimuli, whereby the latter is carried by cells in the BLA that express the cholecystokinin marker (CCK, Shen et al., 2019). In addition, Ppp1r1b+ and Rspo2 mark neurons that are preferentially activated by reward-related or aversion-related stimuli (Kim et al. 2016, 2017). The latter project onto D2R-MSNs and may code for aversive valence. The BLA projects also to the central nucleus of the amygdala (CeA) mediating both appetitive and aversive valence, the later though Respo+ neurons (Kim et al. 2016). CeA in turn sends GABergic projection to the LH, the VTA, the pedunculopontine nucleus (PPN) and the periaqueductal grey (PAG). Pharmacological blockade of CRF1 receptors in the CeA blocks the aversive nature of opioid withdrawal (as measured by the effect on CPP), but only minimally affects other withdrawal symptoms (Heinrichs et al. 1995)(Koob 2019). Recent evidence suggests that a population of excitatory, vesicular glutamate transporter 2 (vGluT2)-expressing neurons in the mouse median raphe region (MRR) orchestrate the activity in downstream aversion centers (Szőnyi et al. 2019). An aversion circuit that converges onto D2R-MSNs is thus emerging, and it may drive the negative reinforcement in 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). During cocaine withdrawal, the time of immobility is longer in the forced swim test, a test for depression-like behavior. This behavioral state has been linked to a synaptic potentiation of the LHb to the RMTg projection by insertion of GluA1subunit of AMPA receptors (Meye et al. 2015) Taking advantage of this mechanistic insight, a selective inhibition of membran insertion of GluA1 insertion also blocks depression like behavior during withdrawal, suggesting a link of causality.

Additional transmitter systems may also play a role. For example, dynorphin, which is produced by D1R-MSNs, is upregulated during withdrawal, inducing dysphoria *via* 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 dorsal striatum (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 "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) but also to the ventral pallidum (VP), while D2R-MSNs of the 'indirect-pathway '(also labelled 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-MSN were depressed mediate sensitization and impaired processing of natural reward, respectively. The VP thus emerges as a potential hub for the integration of postive and negative reinforcement (Wulff et al. 2019). The two populations 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 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 recent review see (Ikemoto et al. 2015), eventually relaying the information from the mesolimbic to the nigro-striatal DA projection.

CIRCUITS OF COMPULSION

A leading hypothesis posits that cortico-striatal projections control the transition to compulsion (Everitt & Robbins 2016b; Lüscher et al. 2020). While some studies claim a hypofunction of the prefrontal cortex, of the mPFC in particular (Chen et al. 2013), others found a hyperactivity of the orbitofrontal cortex (OFC) to dorsal striatum 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 made up 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 the medial precentral area (area 9,10, (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/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 (mDST).

The OFC comprises the anterior and ventral part of the PFC and is subdivided into a medial and a 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 5 gyri limited by the insular cortex, located caudally. Areas 11, 10, and 47/12 are made of 6 layers and are considered granular cortex, while areas 13 and 14 range from agranular to dysgranular (Öngür et al. 2003). In *non-human 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 is divided into four main regions: the medial orbital (MO) region, the lateral orbital (LO) region, the ventro-orbital (VO) region, and the dorsolateral orbital (dLO) 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 dorsal striatum as well as the hypothalamus and peri-aqueductal gray (PAG).

As stated above, outputs from the mPFC thus reach the ventral parts of the striatum, while the OFC preferentially connects to the dorsal striatum. 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 where 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 substantia nigra pars compacta (SNc) in the process, giving off ascending projections to more and more lateral parts of the dorsal striatum (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 dorso-lateral parts of the DST.

CORTICAL CONTROL OF DECISION MAKING

Based on lesions, 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 the working memory, to store 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. 2018). 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 to obtain a reward in a precisely timed fashion, 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 Gage (Macmillan 2000), has motivated many studies in humans, non-human 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 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 between the two levers has become proficient, 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 start performing the behavior that had previously proven useless instead. 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 outcome (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 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 actions and 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 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 random interval 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 de-valued 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 the 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 random interval 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 takes place in the lateral OFC, while the medial OFC controls the integration of relevant information and the update of the value of rewards or actions.

OFC IN COMPULSION

Given the physiological function of the OFC, its involvement in compulsion is not surprising. Moreover, there is experimental evidence from human imaging studies as well as rodent behavior. For example, PET imaging in cocaine addicts reveals a positive correlation 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 functions after chronic drug exposure: manipulation of OFC activity may restore the insight lost after cocaine SA and affect decision making (Lucantonio et al. 2014). This may have to do with the reset of

excessive overexpectation driven by pathological OFC activity (Schoenbaum et al. 2016)(Lucantonio et al. 2015; Schoenbaum et al. 2016).

The OFC also emerges in unbiased c-Fos screening during compulsive cocaine SA or oDASS (Pascoli et al. 2015). When naïve animals are yoked together with compulsive ones controlled 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. An enhanced OFC activity can also be observed with electrophysiology and calcium imaging. In LFP recordings in rats, the amplitude of theta oscillations is associated with subjective value and cocaine preference (Guillem & Ahmed 2017). 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 dorsal striatum, one of the most prominent output streams, indicates that this enhanced activity is associated with a potentiation of glutamatergic synaptic transmission onto SPNs, both in D1R and D2R-SPNs. This is surprising in the light of the rules for the induction that have been established in brain slices of the dorsal striatum (Shen et al. 2008). They 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. Co-activation of the D1Rs and NMDARs trigger 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 (LTP) window for glutamate afferents onto D2R-MSNs (Iino et al. 2020). Artificially overriding these rules (e.g. by pairing and LTD induction protocol with the pharmacological blockade of D1Rs) efficiently depotentiates OFC to dorsal striatum synapses in compulsive mice and reduces oDASS perseverance in spite of aversive stimuli. Conversely, artificial potentiation in non-compulsive 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 renouncing animals arises remains unknown. An appealing possibility is that that OFC-DS 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 revealed stronger synapses between co-activated cortical pyramidal neurons and neurons in the DST in all mice (Wall et al. 2019) at a stage where compulsion has 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 ngeative reinforcement (**Figure 4**). This process is modulated by several factors. In rodents, the schedule of drug availability has a major impact on the transition to addiction. Extended heroin access, for example, considerably increases heroin choices at the expense of food rewards (Lenoir et al. 2013). Long access vs short access to cocaine is also determinant for resistance to punishment (Pelloux et al. 2007). In addition, withdrawal from heroin also increases heroin choices in non-human 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, as it matters whether the animal is in the home cage for the drug consumption (Caprioli et al. 2009). Interestingly, the effect is opposite for opioids and psychostimulants. Animals that have access to the opioid in their home cage (in fact, the experiment was 23h 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.

Serotonin may play a crucial role in the transition to compulsion by exerting a 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 SERT blockade prevents this transition. In other words, the non-specific 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 similarly slef-administred as cocaine in rats (Roberts 1993) but transition to compulsion has not been tested to date. The cellular mechanism underlying the modulatory affect of

serotonin remains elusive, but a modulatory role of 5-HT 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, ACh released from these cells potentiates DA release of mesolimbic afferents (Di Chiara & Imperato 1988; Lüscher & Ungless 2006; Wise & Robble 2020). 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 GIRK channels, the D2R effectors responsible for dampening their activity. A recent study, where D2Rs were overexpressed in cholinergic interneurons, argues for a causal link to resistance of punishment in a cocaine SA paradigm (Lee et al. 2020).

Stress can amplify drug craving and 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 (HPA), which can predict relapse (Sinha et al. 2006). Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes. The corticoid-releasing factor (CRF) is an additional system that has been implicated in mediating consequences of withdrawal. For example, CRF in the central nucleus of the amygdala (CeA) may underlie anxiety experienced during cocaine withdrawal (Zhou et al. 2004). Increased CRH mRNA levels in the rat amygdala during short-term withdrawal from chronic 'binge' cocaine (Zhou et al. 2003) and CRF-R1 antagonists attenuate stress-induced reinstatement of heroin (and cocaine) seeking in rats (Shaham et al. 1998, 2000).

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 this difference was, however, 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 pre-existing vulnerability of an individual. Interestingly, in genetically very homogenous populations, such as the C57BL6J mouse line, the proportion of compulsive individuals is very similar to the fraction observed in humans.

Behavioral differences between C57BL6 sub-strains exist, including addiction-relevant traits (e.g. C57BL6J seem to have a stronger preference for alcohol than C57BL6N, (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 C57BL6J strain. As a proof of principle for individuality emerging in identical C57BL6N 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. Three scenarios seem therefore plausible to account for behavioral individuality in genetically identical mice: i) remaining minimal residual segregation, as perfect inbreeding is impossible ii) stochastic gene expression and iii) 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 cells that are part of the positive and negative reinforcement circuits, altering its function to modulate 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 homogenenous 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. 2017; 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 few studies 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 miRNAs were found in the striatum compared to 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, albeit not 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 BDNF 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 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, there are new therapies for addiction based on the proposed circuit model are only emerging. Since in the VTA and NAc, metabotropic glutamate receptors (mGluRs) control the removal of CP-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 this 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 to goal to allow an addict to regain control. Optogenetic interventions in humans are still many years off, but, in the meantime, the 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" may be the hic et nunc translation of optogenetics.

A handful of studies provide proof of principle for this approach. For example, low frequency DBS stimulation in combination with a D1R antagonist reverse locomotor sensitization to cocaine as efficiently as optogenetic depotentation (Creed et al. 2015). Both these approaches rely on mGluR-LTD. In the case of optogenetic depotentation, 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 uses intermittent, low frequency stimulation with a pharmacological adjuvant to create a lasting effect.

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

A recent study in rodents indicates that DBS at typical frequency above 100Hz 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. STN DBS amy also reverse escalated cocaine use (Pelloux & Baunez 2013).

CONCLUSIONS AND PERSPECTIVES: A GAIN OF FUNCTION DISEASE

In summary, we have reviewed the studies aiming at elucidating the mechanisms underlying the observation that only a minority of recreational drug users eventually fulfill the diagnostic criteria for the disease (Kessler et al., 2004, Wagner and Anthony, 2002). Although a general theory for addiction (Piazza & Deroche-Gamonet 2014) is still far off, there is reason to be optimistic, as there is substantial conceptual advance. Common beliefs that addiction is a neurodegenerative disease have been superseeded 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 the 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 dorsal striatum. Future therapies will take advantage of such a circuit model to prevent or treat addiction.

BOX: OPEN QUESTIONS

1. ***How does compulsion emerge?*** There is some evidence which circuits control compulsions once it has manifested. However we do know little when these changes emerge and how the individual difference comes about. It there a predisposition that is deterministic or is there are 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 DA imput from the SNc and which eludes the initional 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.

3. ***Which circuit element is best suited for a therapeutic intervention?*** The ideal site of intervention will depend on accessibility as well as effect on addiction behavior. Deep brain stimulation works best when targeting small nuclei with a dense neural population (eg. Subthalamic nucleus for Parkinson's) while magnetic stimulation may be more suitable for cortical regions. Regardless, clinical trials will be challenging, as be the nature of the disease clinical cohorts are difficult to consitute.

FIGURES

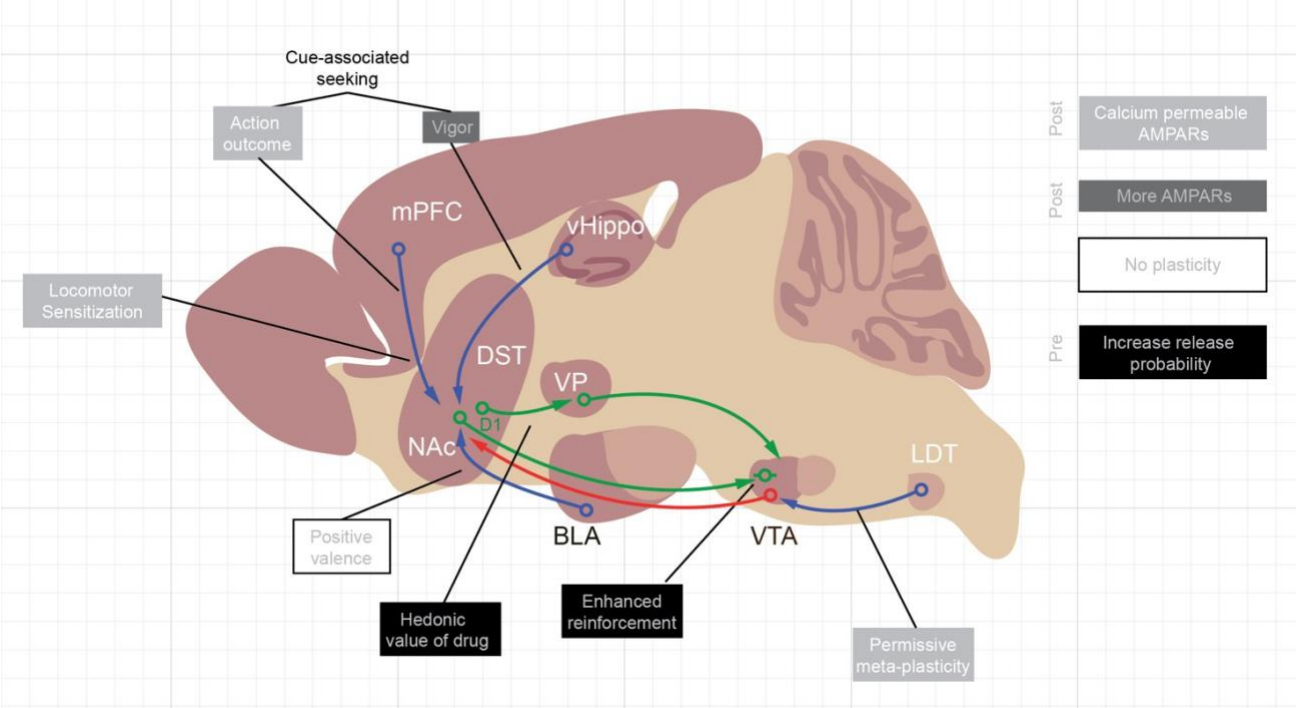

Figure 1. Circuits of positive reinforcement driving early drug adaptive behavior. DA neurons receive excitatory and inhibitory inputs from lateral dorsal tegmentum (LDT) and VTA GABA interneurons, respectively. The projection to the NAc is strongly reinforcing, most prominanly by modulating cortical afferents from the mPFC that inpinge onto D1R expressing MSNs, which project back onto VTA GABA interneurons. Starting with the first exposure to an addictive drug, these dircuits 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.

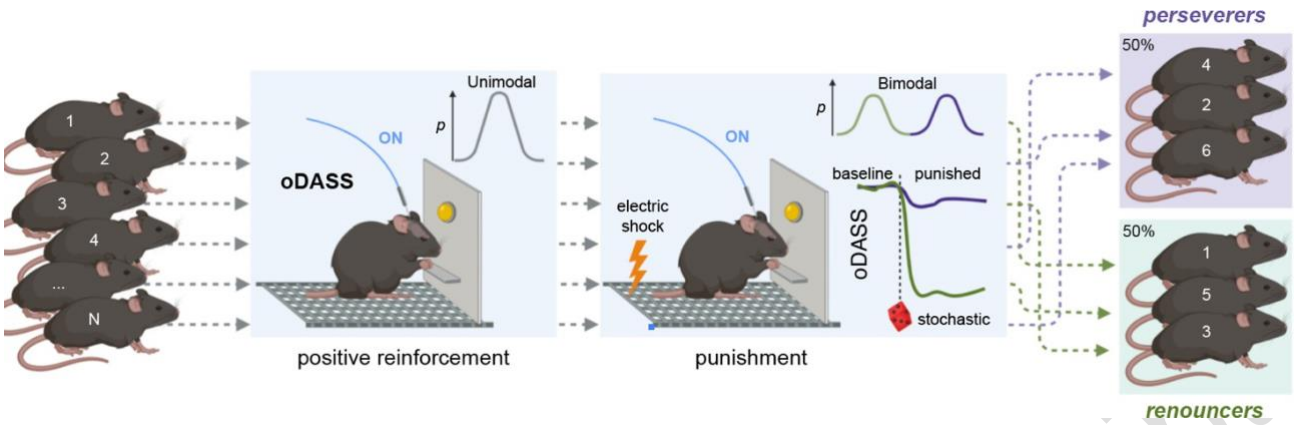

Figure 2. Stochastic transition towards compulsion. Acquisition of VTA DA neurons self-stimulation (oDASS) is unimodally distributed with only little variance. Upon introduction of an aversive stimulus (punishment) some animals renounce oDASS while other continue even when having to endure the negative consequences. As a result a bimodal distribution is emerging. Given the variance, typically 50-100 animals will have to be tested.

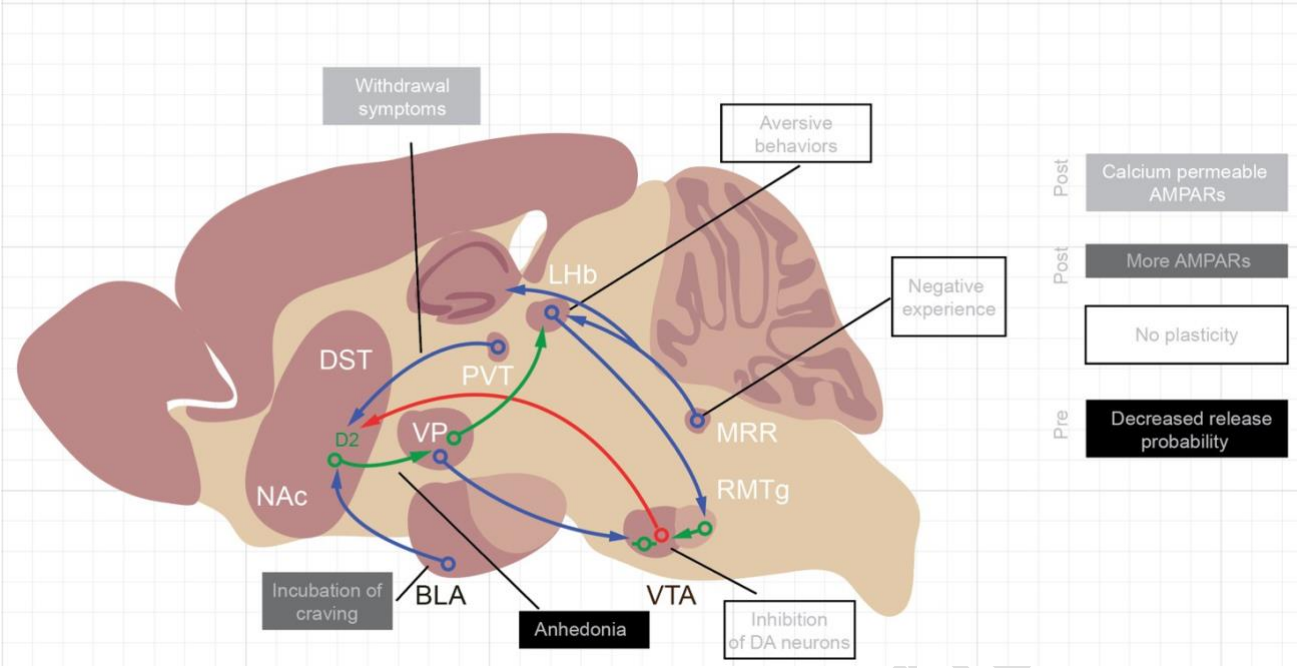

Figure 3. Circuits of negative reinforcement. The median raphe region (MRR) constitutes a hub, which, via the lateral habenula (lHb), reaches the rostral tegmentum (RMTg) where GABA neurons are stimulated that eventually inhibit VTA DA neurons. Other excitatory inputs converge from the basolateral amygdala (BLA, mostly CCK positive neurons) and the perventricular thalamus (PVT) onto D2R-MSNs of the NAc. Anhedonia has been linked to D2R-MSN projections to the ventral pallidum which undergo presynapstic depression upon cocaine withdrawal. Opioid withdrawal symptoms have been linked to plasticity at PVT to D2R-MSN synapses and incubation of craving to potentatioon of BLA afferents onto the same neurons.

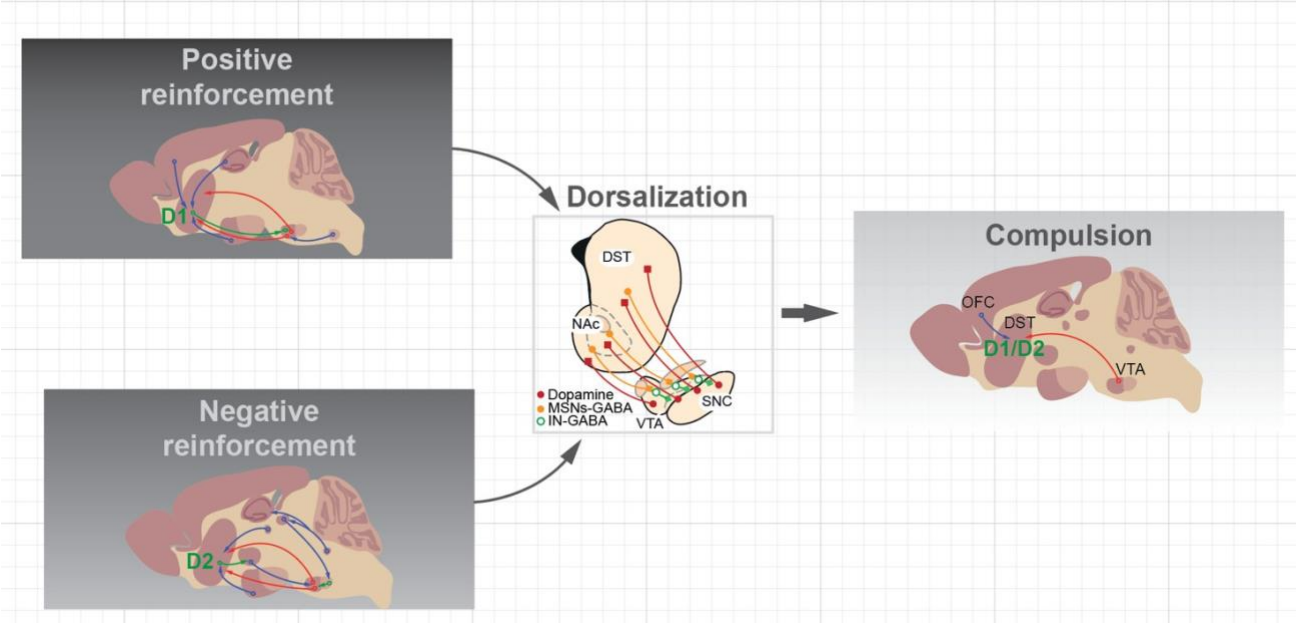

Figure 4. Modular assembly of a consolidated circuit model for addiction. Positive and negative reinforcement add up to drive the dorsalitation. Through the sprialing back projection of MSNs (directly to the midbrain in the case of D1R-MSNs and indirectly via the ventral pallidum for D2Rs) OFC to dorsal striatum circuits are recruited. Compulsion is then expressed by synaptic potentation onto both D1R and D2R-MSNs in vulnerable individuals.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Acronyms and Definitions

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

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

GABA: γ-aminobutyric acid, an inhibitory neurotransmitter

GHB: γ-hydroxybutyrate, a commonly used club drug

DAT: dopamine transporter expressed on the cell membrane for the reuptake of the transmitter from the extracellular space

VTA: ventral tegmental area, a nucleus at the tip of the brainstem with DA projection neurons

RMTg: rostromedial tegmentum, a nucleus adjacent to the VTA made of GABA neurons that inhibit DA neurons

NAc: nucleus accumbens, a nucleus of the ventral striatum that integrates DA inputs from the VTA and glutamate projections from the prefrontal cortex, the amygdala, and the ventral hippocampus**[[**AU: Formatting restrictions limit us to about 20 words per definition. Possible to trim this (currently 28 words)?**]]**

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

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

Resistance to punishment test: a behavioral assay whereby a mild electric shock is delivered when an animal self-administers an addictive drug to assess its motivational value