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Cell-type and projection-specific dopaminergic encoding of aversive stimuli in addiction

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Abstract

Drug addiction is a major public health concern across the world for which there are limited treatment options. In order to develop new therapies to correct the behavioral deficits that result from repeated drug use, we need to understand the neural circuit dysfunction that underlies the pathophysiology of the disorder. Because the initial reinforcing effects of drugs are dependent on increases in dopamine in reward-related brain regions such as the mesolimbic dopamine pathway, a large focus of addiction research has centered on the dysregulation of this system and its control of positive reinforcement and motivation. However, in addition to the processing of positive, rewarding stimuli, there are clear deficits in the encoding and valuation of information about potential negative outcomes and how they control decision making and motivation. Further, aversive stimuli can motivate or suppress behavior depending on the context in which they are encountered. We propose a model where rewarding and aversive information guides the execution of specific motivated actions through mesocortical and mesolimbic dopamine acting on D1- and D2- receptor containing neuronal populations. Volitional drug exposure alters the processing of rewarding and aversive stimuli through remodeling of these dopaminergic circuits, causing maladaptive drug seeking, self-administration in the face of negative consequences, and drug craving. Together, this review discusses the dysfunction of the circuits controlling different types of aversive learning as well as how these guide specific discrete behaviors, and provides a conceptual framework for how they should be considered in preclinical addiction models.

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Keywords

Nucleus Accumbens; Prefrontal Cortex; Cocaine; Self-administration; Punishment; Associative Learning

1. INTRODUCTION

The ability to guide adaptive decision-making in response to environmental stimuli is critical to the execution of appropriate behaviors (Rangel et al., 2008). Aversive learning has evolved as an adaptive behavior to promote survival. This complex process is controlled by circuits across the brain and involves learning the relationship between predictive cues and their outcomes, attributing value/valence to these cues, and using this information to guide seeking/avoiding or initiating/inhibiting behavior at appropriate times (Berridge and Robinson, 2003; Dayan and Balleine, 2002; Berridge, 2012; Skinner, 1958b). Aversive stimuli can act both to inhibit behaviors, where they function as punishers (Solomon, 1964), or to drive motivated behavior as either positive reinforcers (Lolordo, 1969; Weisman and Litner, 1969) or negative reinforcers (Herrnstein and Hineline, 1966), depending on the context in which they are presented. These stimuli can be discrete, as in the case of shock, or more complex, where a particular response in one context results in the presentation of a negative outcome later (Morris, 1987). Thus, parsing out the different neural circuits that control the encoding of valence, motivational drive, behavioral response, and information updating is critical to understanding the basic processes that govern valence-based learning mechanisms. Further, insight into how these different types of learning are dysregulated in disease at a circuit level is fundamental to understanding how this dysfunction ultimately drives pathological behavior.

Drug addiction is a disorder characterized by widespread changes in circuit function across the brain that are involved in a number of behavioral processes, including the encoding of both rewarding and aversive stimuli (Koob and Volkow, 2010; Volkow et al., 2013). Because addiction is often considered in the context of positive and reward-related behaviors such as motivation, drug seeking, and drug consumption, a large amount of work has focused on these behavioral processes and the neural circuits that underlie them (Everitt and Robbins, 2005; Siciliano et al., 2015). However, equally important in the underlying psychopathology of addiction is the dysregulation of behaviors associated with negative/aversive stimuli. How drugs influence the encoding of information and responses to aversive stimuli is a complex process that requires a clear understanding of the different types of aversive learning and the neural circuits involved in mediating behavioral responses to stimuli in specific contexts.

Midbrain dopaminergic pathways are situated at the core of these learning and memory processes. There is a large amount of evidence suggesting that mesolimbic dopaminergic signaling processes both rewarding and aversive information (Lammel et al., 2014; Carlezon and Thomas, 2009; Volman et al., 2013; Salamone and Correa, 2012; Ilango et al., 2014a, b; Vander Weele et al., 2018). In drug addiction, the ability to increase dopamine in reward-related brain regions is critical to the reinforcing effects of drugs of abuse (Roberts et al., 1977; Ritz et al., 1987; Volkow et al., 2004; Melis et al., 2005). This discovery has prompted

an extensive body of work outlining how dopaminergic encoding of reward is altered in drug addiction. In comparison, there is limited information on how dysregulated dopaminergic signaling contributes to the dysregulated learning about negative outcomes that characterize drug addiction. However, emerging evidence has demonstrated that the neural mechanisms mediating aversive learning not only recruit similar brain regions, but that dysfunctions in aversive learning play a key role in the maladaptive behaviors of drug addiction.

Here we outline the dopaminergic circuits that aversive stimuli engage to drive or inhibit behavior in different contexts and provide a framework for how drug exposure disrupts these processes to drive the pathological and maladaptive behaviors that characterize drug addiction. By focusing on different types of aversive learning that either elicit passive responses or require motivated inhibition or initiation of behavior, we define the neural circuits controlling different aspects of aversive stimuli in driving behavior. Further, we shed light on how these circuits are dysregulated in the case of drug addiction and how this dysfunction leads to maladaptive behaviors in response to negative consequences. Together, we hypothesize that rewarding and aversive stimuli guide the execution of specific motivated actions through dopaminergic projections to the nucleus accumbens (NAc) and prefrontal cortex (PFC). Further, we propose that drugs of abuse cause remodeling of these dopaminergic circuits, as well as downstream neuronal populations, driving addictive behaviors.

2. THE BEHAVIORAL RESPONSES ELICITED BY A STIMULUS ARE CONTEXT AND SCHEDULE DEPENDENT

To understand and make valid conclusions about the neural circuit control of behavior, it is first critical to understand how stimuli act to guide behavior in different environments. Overlooking context-specific behavioral control can lead to unclear conclusions and a simplistic understanding of circuits as “reward promoting” or “aversion promoting”. However, years of work in the behavioral pharmacology field has clearly outlined that the value of the stimulus is less of a behavioral determinant than the situation under which the stimulus is encountered (Dews, 1955, 1956). Thus, dissociating circuit encoding of stimulus value from the behavioral action initiated by stimulus presentation is critical to our understanding of neural circuit control of behavior.

Learning about positive and negative outcomes can be passive, where animals learn to associate cues with stimuli and develop conditioned behavior - most often associated with Pavlovian tasks (Blanchard & Blanchard, 1969; Maren, 2001), or goal-directed, where a stimulus-response relationship alters the probability of subsequent behavior - i.e. operant self-administration (Skinner, 1958a, b). In the context of self-administration, behavioral responses are defined by: 1. the probability of subsequent responding, and 2. whether the response results in the presentation or removal of a stimulus (see Figure 1). Reinforcement defines an increased probability of future behavior and can be positive - where a behavior results in the presentation of a stimulus, or negative - where the behavioral response results in the removal of a stimulus. Punishment, on the other hand, is defined by a reduced probability of future behavior and can also be positive - where a behavioral response results

in the presentation of a (typically aversive) stimulus, or negative - where a response results in the removal of a stimulus (typically a reward). It is important to note that an “aversive stimulus” can increase or decrease behavior depending on the schedule of reinforcement in which it is presented (Barrett and Bergman, 2008). Thus, it is important to understand how circuits are engaged during different aspects of motivated action in order to determine if they encode the relative value of the stimulus or the behavioral response to that stimulus.

One particularly important distinction between these paradigms is the difference between negative reinforcement and punishment, as well as what actually defines a punisher. Negative reinforcement is characterized by responding to avoid the presentation of a stimulus, while positive punishment is characterized by inhibiting behavioral responding to avoid the presentation of a stimulus. The classical definition of a punisher is a stimulus that reduces the probability of subsequent behavior. Punishment can be either discrete, where the behavior leads to a consequence like a foot shock, or can be complex, where a behavioral response leads to the removal of a reward in the future (Holland and Skinner, 1961). Second, the stimulus needs to be presented *contingently*. The contingent aspect of this process is often overlooked and is critically important to its control over behavior. For example, random non-contingent footshock presentations are aversive, but not punishers. Similarly, it is tempting to define a stimulus as negative or positive in regard to behavior. However, no stimulus can actually be defined as a “negative reinforcer” or a “positive reinforcer” because all reinforcement is context dependent. A particularly strong example of this is that animals will voluntarily self-administer tail-shock in a schedule-dependent fashion (Byrd, 1969; Stretch et al., 1970; Kelleher and Morse, 1969). Thus, an “aversive stimulus,” such as a footshock, can support negative reinforcement, function as a punisher, and function as a positive reinforcer - all within an individual animal. Together, the action of the stimulus, or the perceived value of the stimulus, is often less of a behavioral determinant than the schedule or context under which the stimulus is presented (Dews, 1955, 1956).

Understanding these processes is critically important, as it allows us to combine these behaviors with neural recordings to dissociate stimulus value from stimulus-driven behavior. Using this approach, we can define the neural circuit encoding of motivation, stimulus value, and the initiation or suppression of actions. Moving forward, it will be important to understand these concepts and go beyond just determining if neural circuits encode “rewarding” or “aversive” aspects of a stimulus. Below, we outline how dopaminergic responses to aversive stimuli in a context-dependent manner control behavior and how this process is dysregulated in addiction.

3. AVERSIVE STIMULI ELICIT BOTH ACTIVE AND PASSIVE BEHAVIORAL RESPONSES

Learning information about contextual cues and aversive stimuli is an important process that guides animals to avoid situations that result in aversive outcomes (Maren, 2001; Maren et al., 2013). This process can be either passive or active (see Figure 2). In passive learning paradigms, animals learn to associate cues with aversive stimuli and develop conditioned behavior such as freezing or avoidance (Blanchard & Blanchard, 1969; Maren, 2001). Active

avoidance of aversive outcomes is more complex and requires motivated inhibition or initiation of behavior, depending on the setting in which these stimuli are encountered (Miller, 1948; Mowrer & Lamoreaux 1946). In the context of operant responding, animals can learn to emit a response to prevent the delivery of shocks or other aversive stimuli, i.e. negative reinforcement (Sidman, 1953; 1962). Conversely, in punishment tasks, animals will learn to inhibit responding (Solomon, 1964). In reinforcement paradigms, these goal-directed responses can be even more complicated, where aversive stimuli themselves function as positive or negative reinforcers depending on the schedule of reinforcement. Therefore, as discussed above, the context in which a cue or stimulus is presented serves to govern the behavioral response of the animal and is a critical determinant of the neural circuits that are engaged.

Each of these variants of aversive learning involves similar brain circuitries, but with important differences that mediate these distinct behavioral responses and rely on the value of the outcome to the behavioral response. For example, the successful avoidance of a negative stimulus is encoded in a similar manner to other positive outcomes within the brain (Kim et al. 2006), suggesting that this type of learning engages both reward- and aversion-based learning mechanisms. In fact, successful avoidance of a negative stimulus leads to increases in dopamine signaling in the nucleus accumbens (NAc), a key brain reward center (Oleson et al., 2012; Wenzel et al., 2015). Along similar lines, if a punisher is introduced when animals are responding for a reward, such as shock upon lever pressing, a conflict is created where both a positive and negative stimulus are presented. In this case, a decision must be made about the relative value of each of the competing signals. In each of these situations, animals have to attribute valence to predictive cues, determine predicted outcomes, and decide to initiate or inhibit behavior depending on the environment in which each cue is presented. Given these complex learning tasks, it is critically important to untangle the neural mechanisms encoding valence, outcome, and motivation independently.

Multiple types of aversive learning have been shown to be dysregulated in drug addiction in both human and animal models and are thought to contribute to compulsive drug use as well as relapse (Robbins and Everitt, 2002; Koob, 2009). Human drug addicts do not value potential negative outcomes of their actions, leading to drug seeking, drug consumption despite negative consequences, and relapse (Burattini et al., 2006; Petry et al., 1998; Grant et al., 2000; Bechera & Damasio, 2001). These same behaviors are seen in animal models. Initially, if a punisher (footshock) is introduced during early phases of drug self-administration, animals will stop taking cocaine. However, after an extended history of drug self-administration, animals will continue to self-administer drugs of abuse, even with increasing foot shock intensity, showing that there is a dysregulation in the balance between the value of the reinforcer and punisher (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004; Pelloux et al., 2007). In some contexts, negative reinforcement can actually be the primary driver of drug consumption. For example, with opioids and alcohol, the withdrawal produces both physical symptoms as well as negative affective states (Koob, 2013; Koob and Le Moal, 1997). In these cases, people will continue taking drug to avoid the negative consequences of stopping use, which is a classical example of negative reinforcement. Thus, to understand drug addiction as a disorder, we need to understand

exactly which aspects of aversive learning are dysregulated by drug exposure, as well as the precise circuits within the brain that are driving these maladaptive behaviors.

4. DEFINING THE CIRCUITS INVOLVED IN AVERSIVE LEARNING

4. 1. Mesocortical and mesolimbic dopamine control active and passive responses to aversive stimuli

The ability of aversive stimuli and associated cues to guide behavior is a learning process, and as such, information has to be updated to predict and drive future behavior effectively and efficiently. There is extensive evidence demonstrating that ventral tegmental area (VTA) dopamine neurons are the main substrate encoding the valence of stimuli as well as the ability to predict the presentation of future stimuli (Bayer and Glimcher, 2005; Roesch et al., 2007; Lak et al., 2014; Pultorak et al., 2018). For example, activity of VTA dopamine neurons serves to predict stimulus value (Schultz et al., 1997; Schultz and Dickinson, 2000). Initially, dopamine cell firing is increased in response to the presentation of unexpected rewards. However, when a cue representing a reward of a particular predicted value is presented, dopamine neuron firing is increased to the cue, but not to the reward presentation, acting to update information and refine future behavior via “error signals” (Schultz et al., 1997). If the value of the stimulus that the cue preceded was different than the predicted value, there will be a subsequent dopamine signal to the stimulus itself. If the stimulus value is less than expected, dopaminergic firing will decrease, and if it is greater than expected, VTA dopamine neuron firing will increase. This acts to feed-back and change the neural response to the cue, refining expectations to allow for adaptive behaviors - either avoidance or seeking. While these dopaminergic circuits have been studied extensively in reward, there is a large body of evidence that they are regulated by aversive stimuli as well. In the case of rewarding versus aversive stimuli, one hypothesis is that bidirectional and temporal differences in dopamine firing in single projections encode the value of incoming information. However, there is also evidence that aversive stimuli increase VTA firing rates in a subset of dopamine neurons, which has led to the hypothesis that there are functionally distinct populations of dopamine neurons that encode reward and aversion (Brischoux et al., 2009; Lammel et al., 2012, 2014; Morales and Margolis, 2017; Breton et al., 2018). There is evidence for the validity of both these processes and it is likely that they work together to efficiently drive behavior in response to rewarding and aversive stimuli.

4. 2. The Lateral Habenula and RMTg are critical mediators of VTA activity

In order for VTA dopamine neurons to be differentially modulated upon the presentation of rewarding or aversive stimuli, upstream signals are integrated to determine when cells will fire and which cells are activated/inhibited. The lateral habenula (LHb) serves as an integration center for information to the limbic system, influencing behavior, learning and memory (Geisler and Trimble, 2008; Hikosaka, 2010), especially in the context of neural responses to aversive stimuli. LHb neurons are glutamatergic neurons that project to the VTA, synapsing on both GABAergic neurons [in the rostromedial mesopontine tegmental nucleus (RMTg)], also called the tail of the VTA, and dopaminergic neurons in the VTA (Omelchenko et al., 2009; Beier et al., 2015; Lammel et al. 2012). The RMTg neurons project to the VTA, producing a strong inhibitory influence over VTA dopaminergic

neuronal activity (Jhou et al., 2009). LHB neurons preferentially synapse on RMTg GABAergic neurons and mesocortical VTA dopaminergic neurons that specifically project to the medial prefrontal cortex (mPFC), rather than the mesolimbic neurons projecting to the NAc (Lammel et al., 2012), providing a mechanism by which stimuli can selectively modulate the VTA bidirectionally or activate divergent populations of dopamine neurons at appropriate times.

4. 3. D1- and D2-type neurons are at the hub of dopaminergic information encoding

The mesolimbic and mesocortical dopamine systems both originate in the VTA and synapse in the ventral striatum and prefrontal cortex, respectively. The VTA's central role in learning and memory processes is driven by its ability to send signals and coordinate activity of downstream brain regions through dopamine signaling (Morales & Margolis, 2017; Tsai et al., 2009; Creed et al., 2014). While there is evidence that divergent dopaminergic pathways encode rewarding/aversive stimuli (discussed in detail below), there is also diametric encoding of rewarding/aversive stimuli within each projection region, which is achieved through the pathway and cell-type specific neuromodulatory effects of dopamine on downstream neuronal populations.

Dopamine is a neuromodulatory neurotransmitter that acts through G-protein-coupled receptors and as such, its role is to act as a high-pass filter in downstream neural populations (Surmeier et al., 2007; Gerfen and Surmeier, 2011; Neve et al., 2004), enhancing the probability of action potential firing in response to high-frequency inputs while minimizing responses to low-frequency inputs (Hiroshi and Schuman, 2007). D1 receptors are Gq coupled and increase the probability of driving action potential firing in response to signals from afferents synapsing onto the D1 containing cell (Wang et al., 1995; Neve et al., 2004). Conversely D2 receptors are Gi coupled, and dopamine acting on these cells suppresses calcium currents, resulting in decreased excitability (Hernández-López et al., 2000; Neve et al., 2004). Thus, dopamine can modulate multiple populations of neurons, resulting in opposite effects on the neurons themselves as well as their ability to drive activity in downstream projection targets (Surmeier et al., 2007). While D1 and D2 receptors display some degree of colocalization in the PFC (Vincent et al., 1995), in the NAc, D1 and D2 receptors are located on largely non-overlapping populations of medium spiny neurons (MSNs) (Kupchik et al., 2015) and have been shown to drive different behavioral outcomes, with D1 MSN activity driving reward-related behaviors and D2 MSN activity driving aversion (Calipari et al., 2016; Lobo et al., 2010). Although the literature is rich in information on the role of VTA activity and dopamine itself in encoding information, there has been less investigation into the specific role of D1- and D2-containing neuronal populations in guiding behavior. With recent advances in genetic and optical tools, we are now starting to be able to parse apart the contributions of dopamine and upstream and downstream circuits in both normal and maladaptive learning processes (Kravitz et al., 2012; Lüscher et al., 2015; Tye and Deisseroth, 2012; Steinberg and Janak, 2013).

To summarize, the VTA receives information regarding conditioned or unconditioned aversive stimuli from thalamic nuclei such as the LHB and relays this information via its dopaminergic projections to the NAc and the mPFC, the two main sites determining current

and future behavior. Overall, this mesolimbic/mesocortical neural circuit supports both the emotional (e.g., fear) and cognitive (e.g., error prediction) aspects of passive aversive learning in specific contexts. Understanding the role of dopaminergic activity and its effects on downstream populations is critical, as drug exposure has been shown to dysregulate the molecular and circuit dynamics of these populations as well as their ability to guide goal-directed behavior (Ferris et al., 2013; Lüscher, 2016; Wright and Dong, 2017). Here we will outline how aversive learning specifically gates activity of independent populations of neurons in different brain regions and how these processes are important in gaining a comprehensive view of the pathophysiology of addiction.

4. 4. Dopaminergic Circuits Controlling Passive Aversive Conditioning

One of the simplest forms of aversive learning is one in which animals passively learn to associate a noxious/aversive stimuli with a specific cue or context. In these situations, animals do not have to emit active behavioral responses; rather, the responses are often reflexive, thus providing an excellent platform for outlining the initial pathways involved in learned information about aversive stimuli. Experimentally, these Pavlovian learning paradigms can be represented with behavioral models such as conditioned place aversion (CPA) and fear conditioning (see Figure 2), where animals learn the association between a conditioned stimulus and an aversive unconditioned stimulus. The neural circuitry responsible for the association of the conditioned stimulus and unconditioned stimulus as well as the expression of fear response is well characterized. The proposed neural pathways mediating the various aversive learning paradigms are shown in Figure 3.

As the gateway to the mesolimbic and mesocortical dopaminergic circuit, the VTA is also fundamental to encoding aversive stimuli and their associated cues. Acute aversive stimuli produce rapid increases in the activity of dopaminergic neurons within the VTA (Moriya et al., 2018). However, aversive stimuli can also produce inhibition of VTA dopaminergic neurons (Jhou et al., 2009b). The appearance of both excitatory and inhibitory responses in VTA neurons suggests that the VTA responds bidirectionally based on the location of the dopaminergic neuron within the VTA (Tye et al., 2013; Brischoux et al., 2009). It is possible that distinct populations of dopamine neurons reside within the VTA and drive behavioral responses to aversive stimuli through discrete patterns of activation or inhibition. Emerging evidence supports this hypothesis. When aversive stimuli are presented, reward-predictive dopaminergic neurons are inhibited, while a distinct population of dopaminergic neurons are excited (Matsumoto and Hikosaka, 2009). In rats and non-human primates, dopaminergic neurons in the dorsal portion of the VTA respond to rewards or reward cues, whereas the ventral VTA responds to footshocks (Brischoux et al., 2009; Matsumoto & Hikosaka, 2009), suggesting that different populations of dopamine neurons may be both functionally as well as spatially separated, at least in part, within the brain. In fact, it is likely that these populations of dopamine neurons also have different projection targets. For example, dopaminergic projections from the VTA to mPFC have been shown to be one of the primary pathways activated by aversive stimuli (See Figure 3; Luo et al., 2018; Lammel et al., 2012, 2011). Further, optogenetic inhibition of tyrosine hydroxylase (TH)-positive cells in the VTA show that neural ensembles projecting VTA-mPFC are critical for fear recall (Luo et

al., 2018). Thus, stimuli with divergent valence drive the activation of specific subsets of neurons that bias towards mesolimbic or mesocortical systems.

4. 5. Upstream projections gate specific VTA population activity to rewarding and aversive stimuli

Activation and inhibition of the VTA dopaminergic neurons projecting to divergent targets can occur through selective gating via upstream neuronal activity. LHb neurons preferentially synapse on RMTg GABAergic neurons and VTA dopaminergic neurons that specifically project to the mPFC, rather than the NAc, providing a mechanism by which stimuli can selectively activate populations of neurons. LHb neurons can be excited by both aversive stimuli as well as the cues predicting aversive stimuli (Hikosaka, 2010). This LHb-VTA-mPFC projection is implicated in aversive learning, as phasic stimulation of these neurons is sufficient to induce strong CPA in mice (Lammel et al., 2012). This pathway is also involved in aversive aspects of drug addiction, such as the negative affective state associated with withdrawal from opiates. For example, animals will form CPA for environments that are associated with withdrawal symptoms, however, upon administration of tetrodotoxin into the LHb, morphine-withdrawal-mediated CPA is abolished (Wang et al., 2017). The dysregulation of upstream gating mechanisms in drug addiction causes dysfunctional dopamine signaling in the mesocorticolimbic circuit; however, the story is complicated. For example, acute opioid administration activates VTA DA neurons by inhibiting GABAergic neurons in the RMTg, thus decreasing their inhibitory power (Lecca et al., 2011, 2012; Jalabert et al., 2011) and increasing dopamine release in reward-related brain areas (Spanagel et al., 1990). Meanwhile, acute experimenter-delivered cocaine administration produces increased firing rates in a subset of LHb neurons, while inhibiting a different subset of neurons (Zhang et al., 2013). The effects of cocaine on these aversive circuits is interesting as the main pharmacodynamic action of cocaine is through direct inhibition of dopamine transporter function. Thus, changes in the LHb may be due in part to the aversive nature of experimenter-delivered drug paradigms. This highlights a critically important factor in the determination of drug effects on aversive circuits - the difference between experimenter-delivered and volitional intake. Additionally, it is possible that initial cocaine exposure may briefly inhibit some LHb neurons, but shortly after excite a subset of LHb neurons, which could drive the acute effects versus the withdrawal effects. Potentially more important than the acute effects of drugs is the neural plasticity that is induced following repeated drug exposure. Repeated exposure specifically potentiates LHb-RMTg neurons, as opposed to the LHb-VTA pathway (Maroteaux & Mameli, 2012). To complicate matters further, recent studies suggest that chronic drug exposure is associated with potentiation of excitatory inputs into the VTA (Lammel et al., 2014; Borgland et al., 2004; Chen et al., 2008; Dong et al., 2004). Overall, LHb/RMTg gating of VTA dopamine neurons mediates the initial effects of drugs of abuse as well as the plastic changes in downstream dopaminergic neurons seen in chronic drug addiction. This dysregulation may serve to bias activity towards one downstream pathway over the other, altering reward prediction and prediction error signaling (Hyman, 2005) and contributing to compulsive drug-seeking behavior.

4. 6. Dopamine gates downstream neurons that encode information via D1 and D2 receptor expressing neurons.

Changes in the balance between mesocortical and mesolimbic systems may be a critical factor in driving adaptive learning based on rewarding and aversive stimuli. It is also important to understand how bidirectional fluctuations in dopamine levels in each projection target can lead to the excitation and inhibition of downstream D1- and D2-containing neuronal populations and how the activation of these neuronal population within the NAc or mPFC may control some aspects of aversive learning.

Dopaminergic projection to the PFC and the role of D1 and D2 receptors—As a downstream target of the VTA, dopaminergic signaling in the mPFC is involved in modulating attention towards cues and consolidating memory in aversive learning (Pezze et al., 2003; Gonzalez et al., 2015). Microdialysis in the PFC shows that stressors, including tail-shocks, enhance dopamine levels in the PFC (Abercrombie et al., 1989). However, this enhancement of dopamine levels in the mPFC may not necessarily translate into increased neuronal activity, as it has been shown that dopamine can inhibit neuronal activity in the mPFC (Trantham-Davidson et al., 2004). It is likely that dopamine signaling biases towards activation of certain cell types while inhibiting others through its action on D1 and D2 receptors, which can be expressed at different levels on different output populations. There is some evidence that differential activation of D1 or D2 receptors in the mPFC results in discrete encoding of stimuli. For example, D1 receptor antagonists infused into the mPFC prevent the association of specific contexts with aversive stimuli, despite stimulation of the LHB-VTA/RMTg neurons (Lammel et al., 2012), suggesting that signaling onto downstream D1 and D2 receptors in the mPFC are critical for processing of information. Together, these results suggest that dopaminergic activation of the mPFC serves to mediate passive aversive learning by consolidating memory of the association between cues and stimuli.

The dysregulation of dopaminergic tone and function in addiction has important implications for the functionality of the mPFC and its ability to mediate memory consolidation. Acutely, drugs of abuse, as well as drug-related cues, stimulate dopamine increases in the mPFC, similar to that seen with highly palatable food or reward-predicting stimuli (Bassareo and Di Ciana, 1997; Bassareo et al., 2007). In chronic drug exposure, however, self-administration of cocaine is associated with depressed excitability of the PFC in humans (Chen et al., 2013; Goldstein & Volkow, 2002, 2011) and reduced dopamine tone in rodent models of drug addiction at baseline (Parsons et al., 1991). This reduction in dopamine tone suggests impaired memory consolidation and prediction error signaling, this dysregulation is also critically involved in inappropriate decision making and behavioral choices, which we will discuss further in Section 5. It is important to note, that in addition to reductions in basal dopamine levels, dopamine release in response to cocaine-associated stimuli is enhanced (Parsegian & See, 2014). Moving forward it will be important to determine the roles of basal dopamine levels versus stimulus evoked dopamine levels in guiding motivated behaviors.

4. 7. Dopaminergic population in the NAc and the role of D1- and D2- containing neuronal populations

In addition to the mPFC, the VTA modulates reward and aversive processing through its connections with the NAc (Hu, 2016). VTA projections to the NAc encode both fear expression and fear extinction, as well as updating of prediction errors and instrumental learning processes (Borowski & Kokkinidis, 1996; Badrinarayan et al., 2012; Pezze & Feldon, 2004; Abraham et al., 2014; Luo et al. 2018; Schultz et al., 1997). Specifically, optogenetic inhibition of the dopaminergic VTA-NAc projection results in decreased fear extinction (Luo et al., 2018), mediated mainly by the NAc-shell. In particular, D1-type receptors in the NAc core are critically involved in memory consolidation during Pavlovian tasks, while passive avoidance memories preferentially activate D2-type receptors in the NAc core (Managò et al., 2009). Additionally, D2 receptor activation in the NAc is critical for the formation of aversive learning, as inhibition of these receptors impairs learning in a one-trial avoidance task (Hikida et al., 2013). While earlier studies depict a complex picture of the role of D1 and D2 containing neuronal populations in learning (Riedel et al., 1997; Jongen-Rêlo et al., 2003; Parkinson et al., 1999; Levita et al., 2002), studies utilizing optogenetics and calcium imaging have refined the story further. Information encoding in the NAc is a complex balancing act between D1- and D2-receptor-containing MSNs and the various input/output connections to the NAc (Yang et al., 2018; Koo et al., 2014; Poyraz et al., 2016; Gallo et al., 2018; Al-Hasani et al., 2015; Calipari et al., 2016). Despite the complexities of this system, the NAc is likely to be heavily involved in predicting the presence or absence of fearful stimuli, potentially as an error detection mechanism. Fear-eliciting CS presentation increases dopamine transmission in the NAc-shell while decreasing dopaminergic activity in the NAc-core (Badrinarayan et al., 2012), suggesting that bidirectional dopamine signaling in the NAc as a whole may be involved in encoding both positive and negative information. This may be due to shifting the balance between D1 and D2 MSNs, where high dopamine levels lead to enhanced D1 MSN activity and promote reward, and low dopamine levels bias towards increased D2 MSN activity and promote aversion. However, future studies using optogenetics, genetic identification of neurons, and circuit-based techniques will be critical in clarifying the complicated roles of D1- and D2-containing MSNs in these processes.

The divergent populations of MSNs in the NAc have been implicated in both the reward- and aversive-learning aspects of drug addiction (Lobo et al., 2010; Calipari et al., 2016; Creed and Lüscher, 2013; Bock et al., 2016; Creed et al., 2016). Optogenetically stimulating D1 MSNs is sufficient to induce conditioned place preference (CPP), while stimulating D2 MSN populations causes CPA. Further, optogenetically stimulating D2 MSNs reduces motivation for cocaine, highlighting the role of MSNs in volitional drug consumption (Bock et al., 2016). It is likely that the balance between the activity of these two populations of neurons is critical in encoding rewarding and aversive components of stimuli within the NAc, and that this process is regulated by incoming dopamine signals from VTA projections. Indeed, acute cocaine administration - which increases NAc dopamine levels - preferentially enhances D1 and suppresses D2 NAc MSN activity (Calipari et al., 2016), forming the basis of cocaine-context association learning. Further, long-term drug use is known to result in dysregulation of this system in both humans and in rodent models of

addiction. Chronic drug exposure preferentially biases towards D1-mediated signaling by selectively increasing glutamatergic inputs onto D1 MSNs and enhancing their response to drug associated cues (MacAskill et al., 2014; Calipari et al., 2016; Pascoli et al., 2014; Dong et al., 2004, outlined in detail in Figure 4), an effect that drives drug seeking. Interestingly, recent work shows that increasing the expression levels of D2 receptors in D2-MSNs the NAc - an effect that would reduce neuronal activity in D2 MSNs - is also associated with increased motivation (Gallo et al., 2018), further suggesting that the balance between D1 and D2 MSN activity in reward-related brain regions may be a critical factor that increases the rewarding effects of drugs and associated cues. However, recent work has shown that D2-MSN optogenetic stimulation can either potentiate food self-administration (Soares-Cunha et al., 2016; 2018) or reduce cocaine self-administration (Bock et al., 2016), suggesting that, as with all environmental stimuli, the ability of these populations to regulate motivation may be context- and reinforcer-specific.

Interestingly, while the initial reinforcing effects of cocaine and the associated neuronal regulation of D1- and D2-containing MSNs is dependent on dopamine released into the NAc (Roberts et al., 1977; Ritz et al., 1987), following long-term drug exposure, there are robust deficits in dopamine release both at baseline and in response to cocaine-associated cues (Volkow et al., 2004; Calipari et al., 2012; Siciliano et al., 2015; Ferris et al., 2012; Hurd et al., 1989; Willuhn et al., 2014). Concurrent with this dopaminergic deficit is the enhancement of both excitatory drive onto D1 MSNs and D1 MSN responses to drug associated cues (MacAskill et al., 2014; Calipari et al., 2016). Thus, it is possible that chronic drug exposure remodels these circuits, leading to an inability of dopamine to cause changes in these downstream populations and resulting in reduced behavioral flexibility. Together, these data suggest that the D1 MSN drive becomes less dependent on increased dopamine levels and more dependent on other incoming excitatory inputs in this region. This may have important implications for the ability of the NAc to regulate extinction of drug cue-reward memories, even after prolonged withdrawal.

5. INFORMATION ABOUT AVERSIVE STIMULI IS USED TO DRIVE MOTIVATED BEHAVIOR.

As discussed above, fear learning is an essential adaptive survival mechanism. Once a cue or context is determined to be aversive, it gives rise to variety of avoidance behaviors, which results in vastly more complicated neural responses to aversive stimuli. Not only does the aversive stimulus need to be processed by the brain, but the animal has to use this incoming information to drive escape or avoidance. Successful avoidance of the aversive stimuli can recruit reward circuitry and is therefore encoded, at least in part, as rewarding. For example, while a cue predicting an inescapable shock decreases NAc dopamine release, a cue predicting safety increases dopamine release (Oleson et al., 2012; Badrinarayan et al., 2012). Importantly, avoidance of fearful or aversive cues and contexts can be utilized to reinforce operant behaviors, a phenomenon described as negative reinforcement (Skinner, 1969; see Figure 1). While understanding the neural circuits driving passive aversion learning is critical from a basic learning and memory standpoint, a comprehensive view of how aversive stimuli and associated cues are used to motivate behavior through the activation of reward

and aversion circuits is necessary in understanding the driving forces behind appropriate responses as well as how maladaptive signaling gives rise to inappropriate behaviors.

5. 1. The balance between mPFC and NAc projections is critical for active responses to aversive stimuli

The neural circuitry involved in negative reinforcement requires integration of both aversive- and reward-learning pathways. Negative reinforcement is a form of active avoidance behavior, as it is the removal of an aversive stimulus that drives the motivated behavioral response (Skinner, 1958a, see Figures 1 and 2). Initial exposure to the aversive stimuli and associated cues triggers a fear response, mediated by the aversive-learning circuit. Subsequent learning of the correct avoidance response engages many of the same pathways as rewards, and thus recruits systems that increase the probability of the action being done again subsequently. As with rewards, animals are motivated to press a lever for the avoidance of a shock. Phasic release of mesolimbic dopamine reflects the influence that rewards have on self-initiated operant behaviors (Wassum et al., 2012), and as such, mesolimbic dopamine release occurs upon the successful avoidance of shock and acts to reinforce future behavior (Oleson et al., 2012). Similar to passive aversive learning, active responses to aversive stimuli also recruit the LHb (Stamatakis and Stuber, 2012), which gates the activity of VTA/RMTg neurons, and controls the encoding of information as well as behavioral responses (Proulx et al., 2014). As such, the mesolimbic dopaminergic system is critically involved in this active learning paradigm, and the projections from the VTA to both the mPFC and NAc govern the learning and motivational aspects driving appropriate behavioral responses.

During active avoidance learning, dopamine is increased in the mPFC and NAc (McCullough et al., 1993; Salamone, 1994; Stark et al., 1999, 2000) and is involved in the expression of escape/avoidance behaviors (Oleson et al., 2012; Sokolowski et al., 1994; Stark et al., 1999). Numerous studies have shown that pharmacological inactivation or dopamine antagonists administered to these regions impair avoidance learning and active avoidance responses. For instance, pharmacological inactivation of the mPFC, as well as several other related brain structures, such as the basolateral amygdala (BLA) and ventral striatum results in impaired signaled shock avoidance expression (Poremba & Gabriel, 1999; Bravo-Rivera et al., 2014, 2015; Moscarello & Le Doux, 2013). Further, disrupted communication in the mPFC-BLA network biases motivated behavior to riskier options, suggesting that this circuit is involved in encoding behavioral outcomes as well as impulsive decision-making (St Onge et al., 2012). In active aversive learning paradigms, the mPFC serves to encode stimulus-cue association memories as well as learn and direct behavior to avoid the aversive stimulus. However, because the mPFC governs a variety of different aspects of active aversive learning, its role and pattern of activation in the mesolimbic dopamine circuit is complicated. For example, mPFC principal neurons are disinhibited through activation of the BLA to elicit freezing behavior to aversive cue presentation (Courtin et al., 2014); this suggests that during instrumental learning tasks such as negative reinforcement, these same mPFC neurons are required to suppress amygdala-mediated freezing behavior elicited by aversive stimuli and guide behavior to active responses that will result in avoidance of the aversive stimuli (Moscarello and LeDoux, 2013). Meanwhile,

other projection neurons from the mPFC, such as those to the ventral striatum (Bravo-Rivera et al., 2014; 2015) and NAc (Lee et al., 2014; Mateo et al., 2017), are activated by negative reinforcement tasks and avoidance behaviors. Therefore, the mPFC likely encodes cue-stimulus association memories as well as gates behavior through differential activation and inactivation of various neuronal populations with opposing projection targets. This differential activation of cortical projections could be achieved, at least in part, through dopamine release within cortical regions.

As opposed to the limited role that the NAc plays in passive aversive learning paradigms, its engagement during active instrumental learning is critical for appropriate behavioral responses. Transient dopamine release events signal not only the subjective value of a cue presentation, but also represent the value of avoiding harm (Pultorak et al., 2018). D1- and D2-type receptors are both implicated in active avoidance learning, but mediate differential effects on behavior, as seen by studies in which specific receptor blockades changed conditioned avoidance responses in animals. Dopamine antagonists injected into the NAc impair active avoidance conditioning, but while D1 antagonists reduce both acquisition and conditioned responding in subsequent trials (Wietzikoski et al., 2012), D2 antagonists only reduce subsequent conditioned responding (Boschen et al., 2011). This suggests that D1 receptors mediate the rewarding effects of avoiding noxious stimuli, while D2-type receptors may play a role in learned behavioral responses to aversive stimuli. However, as animals learn to successfully avoid the aversive stimulus through conditioned avoidance responses, dopamine release increases and preferentially activates D1 receptors, which increases D1 MSN activity, thus encoding safety signals similarly to appetitive rewards (Oleson et al., 2012). Instrumental learning and active avoidance responses to aversive stimuli produce dual processing within the NAc, through the differential gating of D1- and D2-like receptor activation - and associated changes in MSN neuronal activity - in order to mediate the passive fear associated with the noxious stimuli (or its associated cue), initiate motivated avoidance behavior, and subsequently encode this successful avoidance as a rewarding outcome.

Overall, aversive learning and the motivated behavior driving avoidance are encoded in the brain through the simultaneous recruitment of reward- and aversive-learning circuits and decision-making circuits. These processes are adaptive, as animals need to be able to learn from past experiences and act in the future to avoid situations in which they might be harmed. However, in drug addiction, negative reinforcement plays a large role in the drive to avoid withdrawal symptoms and may be a large factor in the difficulty in stopping drug consumption once it has begun. It has been shown that animals will form CPA for a drug withdrawal-paired context, highlighting that withdrawal symptoms are aversive on their own (Wang et al., 2017). Further, withdrawal from many drugs of abuse causes anhedonia (D'Souza and Markou, 2010; Martinotti et al., 2008; Markou and Koob, 1991). It is hypothesized that while initial drug exposure is driven by rewarding experiences (i.e. positive reinforcement), over time the motivation to avoid withdrawal (i.e. negative reinforcement) drives a portion of motivated responding (Koob, 2013), at least for drugs with pronounced withdrawal symptoms such as opiates and alcohol. This shift in motivational drive may come from a remodeling of the neural circuits governing these two processes. For example, withdrawal from cocaine changes the membrane excitability of LHb

neurons, resulting in increased excitability and membrane resistance (Neumann et al., 2015), ultimately increasing the response of the LHb to incoming signals and biasing the response of the mesolimbic dopaminergic system in general. Additionally, addiction is associated with decreased basal activity in the PFC during withdrawal (Volkow et al., 2003), which is therefore thought to play a role in craving and relapse (Goldstein and Volkow, 2011). As such, dysregulation of these mechanisms results in maladaptive behaviors and the inability to predict or respond appropriately to situations with negative outcomes. While negative reinforcement may contribute, at least in part, to continued drug consumption, there are a large number of aspects of addiction that are not captured by negative reinforcement models, such as why people relapse once they successfully detoxify or why drugs with minimal withdrawal symptoms still show compulsive consumption.

5. 2. Punishment at the interface between aversive learning and drug addiction

Drug addiction involves chronic dysfunction of dopaminergic circuits - both mesocortical and mesolimbic (Wolf, 2016). At the core of this dysregulation is inappropriate encoding and learning of aversive stimuli, reduced reward associated with successful avoidance, and maladaptive responses in punishment tasks (Bechara, 2005; Di Chiara, 2002; Schultz, 2011). The inability to properly assign value to aversive consequences that occur as a result of compulsive drug seeking or consumption underlies a large aspect of addiction and relapse. Compulsive behavior is defined as performing an act persistently and repetitively without consideration of outcome (Robbins et al., 2012; Gillan and Robbins, 2014). In the context of drug addiction, “compulsive drug use” is most often studied as continued drug use despite negative consequences. This behavior is widely observed in human patients suffering from drug addiction, where they will continue to compulsively seek and take drugs despite financial problems, legal difficulties, loss of friends and family, and even health problems (Yücel et al., 2007; Koob and Le Moal, 1997; Lubman et al., 2004; Hyman & Malenka, 2001). In animal models, animals with a long history of contingent drug exposure will continue to seek and self-administer drugs even when the administration is paired with aversive consequences, such as footshock (Deroche-Gamonet et al., 2004; Vanderschuren et al., 2004; Pelloux et al., 2007). These maladaptive compulsive behaviors in the face of punishment represent a fundamental dysregulation of the neural circuits governing reward and aversion.

Punishment can be either discrete, where the behavior leads to a consequence like a foot shock, or can be complex, where a behavioral response leads to the removal of a reward in the future (Holland and Skinner, 1961). Both engage dopaminergic circuits, which act to assign relative value to cues and responses as well as to initiate action (Schultz, 2005). Drug consumption in the face of a discrete punisher only occurs after long-term high-level drug intake (Deroche-Gamonet et al., 2004; Vanderschuren et al., 2004; Pelloux et al., 2007). Punished behavior is controlled by a complex network of neural circuits encoding information about rewarding and aversive stimuli (see Jean-Richard-Dit-Bressel et al., 2018 for a comprehensive review on punishment). Behavioral responses in punished situations require animals to balance information about an aversive stimulus and a reward simultaneously, and then make a decision about the relative value of the response and associated outcome. This process is critical in normal learning where we regularly make

decisions not to complete certain actions due to either immediate or long-term consequences. However, in drug addiction, the activity and function of the dopaminergic circuits that encode valence, prediction error, and memory are drastically changed, and can lead to decisions to seek out drug, even when the future or immediate consequences are disproportionate to the value of the reward that is obtained.

Because punished responding is a large component of human drug addiction, work has focused on understanding what neural dysfunction could underlie continued drug use/seeking in the face of negative consequences. While acute drug exposure causes increased dopaminergic tone and increased release events in the NAc, a process central to the rewarding value of the drug, chronic drug exposure, especially following self-administration, is accompanied by depleted dopamine levels in the absence of drug, as well as reduced dopaminergic responses to drug-associated cues (Willuhn et al., 2014; Parsons et al., 1991). While in normal situations reduced dopamine levels would result in reduced motivation, these dopaminergic signals in ventral striatal regions seem to be less coupled to motivational drive after drug exposure. Initially, dopaminergic responses to drugs drive drug taking, but over chronic administration, dopaminergic responses to cues and drugs are decreased while the motivational aspects of drugs are sensitized (Calipari et al., 2014, 2013, 2016; Siciliano et al., 2016a, b). This could be explained by the strengthening of downstream pathway activation, which suggests that drug-associated behaviors are less dependent - although not independent - from NAc dopamine increases. These decreases in dopamine release paired with increases in the activity of D1 MSN populations both at baseline and in response to drug-associated cues may lead to the strengthening of drug-associated information at the expense of being able to update these circuits when new information about stimuli are presented. Further, while initial drug-associated information requires activation of ventral striatal regions, such as the NAc core and shell, over long-term repeated use, cues associated with drug availability activate dorsal regions of the striatum, which is thought to drive action initiation to the cue and may elicit habitual action regardless of outcome (Salinas et al., 2016; Willuhn et al., 2012; Everitt & Robbins, 2005; Belin & Everitt, 2008). Therefore, the reduced activity in this area following long term drug use explains why animals do not modify behavior appropriately in the face of punishers or following devaluation of the drug. Together, these neurochemical adaptations ultimately lead to overvaluation of the rewarding aspects of drug-associated stimuli and outcomes and undervaluation of the aversive aspects of drug use.

In addition to the enhancement of reward processing, chronic drug use elicits fundamental changes in brain regions necessary for aversive learning, such as the VTA, mPFC, and NAc (Creed and Lüscher, 2013; Lüscher and Malenka, 2011), as depicted in our model in Figure 4. In the NAc, acute cocaine exposure suppresses GABAergic signaling from D2 MSNs, while enhancing D1 MSN activity, altering the balance between pathway projections from the NAc, particularly to the ventral pallidum (Heinsbroek et al., 2017). Previous work has also shown that D2 activity is associated with aversive outcomes (Kravitz et al., 2012), and that increased D2 MSN firing acts to reduce cocaine consumption in operant tasks (Bock et al., 2013). Reduced D2 outputs, which encode information about aversive stimuli and regulate inhibitory feedback over dopaminergic neuron excitability, serve to decrease feedback mechanisms and cause increased impulsivity and drug-seeking behaviors (Holroyd

et al., 2015). Thus, the decrease in D2 pathway activity may lead to decreased negative effects of the drug as well as decreases in aversive learning in general. Following repeated drug exposure enhanced D1 MSN activity in the NAc shifts the balance towards the D1 MSN output, further promoting drug seeking behavior (Calipari et al., 2016).

Following repeated cocaine exposure, different forms of plasticity are seen in distinct glutamatergic inputs onto D1 MSNs, some of which could explain the observed enhancements in D1 MSN activity. For example, cocaine self-administration increases AMPAR/NMDAR ratios in synapses from the BLA and hippocampal glutamatergic neurons to D1 MSNs (Pascoli et al., 2014; Lee et al., 2013; MacAskill et al., 2014). There is conflicting evidence in regard to mPFC inputs onto D1s, with multiple reports finding modest reductions or no change in AMPAR/NMDAR ratios following cocaine administration (MacAskill et al., 2014; Joffe & Grueter 2016); however, while Pascoli et al., 2014 observed reductions in AMPAR/NMDAR ratios, they also observed increases in excitatory postsynaptic currents (EPSCs), suggesting that the ability of the input to drive D1 activity is increased. These cocaine-driven changes in synaptic plasticity at D1 and D2 MSNs may have long-term impacts on signaling between MSNs and their synaptic inputs and control discrete aspects of behavior. By using optogenetics stimulation protocols to reverse the cocaine-induced plasticity in a synapse specific manner, Pascoli et al., 2014 were able to link hippocampal inputs onto D1 synapses to lever discrimination - i.e. response rates remained high but were not specific to the active cocaine lever. Conversely, they linked mPFC inputs onto D1 synapses to complicated aspects of behavioral performance, where reversing the cocaine-induced synaptic changes abolished lever pressing all together. Together, these data suggest that drug-induced plasticity at specific synapses may carry important and discrete information about value, performance, and motivation; however, more work with complicated behavioral paradigms is needed to define the specific role of each synapse in drug-induced behavior.

The plastic changes in both the mPFC and NAc, due in part to inappropriate signaling from the VTA, lead to long-term alterations in firing properties, which has important consequences for behavior (Pascoli et al., 2014). In fact, optical intracranial self-stimulation of VTA dopamine neurons is sufficient on its own to drive the behaviors that characterize drug addiction (Pascoli et al., 2015). Additionally, electrically evoked dopamine transients in the NAc can influence behavior by triggering cocaine-seeking and self-administration, demonstrating the robust role of dopamine in reinforcement paradigms and addiction (Phillips et al., 2003). Disrupted memory consolidation function by the mPFC prevents subjects from effectively associating the aversive consequences of drugs with the drug itself. This, combined with reduced mesolimbic activity, further potentiates goal-directed actions independent of potential negative outcomes. In the context of drug addiction, the inability to learn about aversive information or how to appropriately avoid adverse situations leads drug users to continue taking drugs compulsively despite numerous negative consequences.

6. CONCLUDING REMARKS

An abundance of research has investigated the neurobiological and behavioral alterations induced by chronic drug use in an effort to describe, understand, and treat the pathology of

addiction. To this end, numerous animal models have been employed, and while some of these models are assumed to accurately recapitulate the phenotypic characteristics of human drug addiction, the development of pharmacotherapies from such preclinical studies has not been effective. It is important to understand the behavioral dysfunction that underlies specific aspects of drug addiction, as well as to understand how brain-wide circuits contribute to these maladaptive behaviors. Goal-directed behavior is complex, is guided by discrete and contextual cues predicting rewarding and aversive stimuli and is context dependent. This contextual information helps animals to guide adaptive decision-making and inhibit or initiate appropriate action at appropriate times. Aversive learning involves passive encoding of stimuli and associated cues, as well as active behavioral responses to avoid these aversive stimuli. Interestingly, many of the brain regions involved in mediating aversive learning are the same regions dysregulated by drug addiction. Understanding the cellular and molecular basis of these processes is fundamental not only as a basic biological phenomenon, but also in relation to treating disorders associated with the dysregulation of these processes. Given the intricacy of these circuits, it is critical to define the subset of neural regions and specific neuronal populations involved in aversive learning in different contexts, as well as provide a framework for understanding the dysregulation of these circuits in drug addiction.

Overall, the reward- and aversive-learning circuits become highly dysregulated during drug addiction, resulting in dysfunctional responding and goal-driven behaviors across a number of contexts. Together, these dysregulations complicate the avenues for treatment, making substance use disorders a vastly complex problem and implicating it as a major issue in today's society. More in-depth studies on the dopaminergic system, dynamics of dopamine and other neurotransmitter signaling, and how these processes are involved in reward- and aversive-learning will be required to not only understand the basic changes associated with drug addiction, but also to find effective treatment options for this disease.

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Highlights:

- Aversive learning is an adaptive survival mechanism involving passive and active responses
- Different aversive learning paradigms activate mesolimbic and mesocortical dopamine circuits
- D1 and D2-containing cell types encode reward and aversion diametrically
- Drug addiction involves maladaptive learning and memory processes
- Dysregulated encoding of aversive stimuli by dopamine signaling dysfunctions drives addiction

Figure 1: Context-specific control of behavior by rewarding and aversive stimuli.

While stimuli such as rewards or footshocks are often defined as rewarding or aversive, it is important to note that their effects on behavior are dependent on the context in which they are presented. Here we outline four different operant behavioral paradigms: positive reinforcement, positive punishment, negative reinforcement, and negative punishment in which the same stimulus can increase or decrease behavior. **(A)** Positive reinforcement is defined by the presentation of a stimulus increasing the probability that subsequent behavior will occur, i.e. a lever press results in food delivery. **(B)** Positive punishment results when the presentation of a stimulus results in a reduction in behavioral responding, i.e. a lever press results in a contingent aversive effect, such as footshock. **(C)** Negative reinforcement is defined by the removal of an aversive stimulus, which increases the probability of subsequent behavior, i.e. a lever press turns off a foot shock. **(D)** Negative punishment reduces behavioral responding because the behavioral response (lever press) results in removal of a positive stimulus, such as food. The difference between these behaviors is critical in understanding how neural circuit responses to environmental stimuli encode information.

Figure 2. Behavioral paradigms for understanding passive and active behavioral responses to aversive stimuli

Here we outline four different aversive learning paradigms: fear conditioning, conditioned place aversion (CPA), negative reinforcement, and punished responding. **(A)** Fear conditioning is a Pavlovian model for passive aversive learning. A foot shock is used as an unconditioned stimulus (US) to elicit a fear response such as freezing, and a tone or other neutral cue is the conditioned stimulus (CS). After several sessions of pairing a tone with foot shock, mice learn to associate the tone with fear and freeze in response to presentation of the tone itself. **(B)** CPA is another passive behavioral model of fear learning used to study drug dependence and withdrawal. It uses an apparatus with two to four chambers, each characterized by different contextual cues. During the conditioning phase, individual chambers are paired with an aversive stimulus or a neutral stimulus. Then, on test day,

animals are allowed access to all chambers and demonstrate preference/avoidance of one of the chambers, depending on which stimuli it was paired with. **(C)** Negative reinforcement is an operant behavioral paradigm in which animals lever press or nose poke to remove or prevent the presentation of an aversive stimulus, such as a foot shock. **(D)** Punished responding is a task where animals are trained to respond for the presentation of a reward. During punishment trials, responses result in both presentation of reward and delivery of an aversive stimulus, such as a foot shock. Punishers reduce response rates as animals learn to omit responding to avoid the aversive stimulus.

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Figure 3: Neural circuits implicated in different aspects of context-dependent aversive learning. Complex networks of brain regions in the mesocorticolimbic dopaminergic system are involved in the encoding of information and behavioral responses in various aversive learning paradigms. (*top*) CPA: Noxious stimuli recruit the LHb, which signals to the mesolimbic dopaminergic system through the VTA and RMTg. Increased dopamine release in the mPFC and decreased dopamine in the NAc mediate avoidance behavior. (*middle*) Fear conditioning: Although similar brain regions as those involved in CPA are activated, unavoidable fearful stimuli drive freezing behavior through the additional recruitment of the amygdala, especially the BLA and CeA. (*bottom*) Negative reinforcement: Active avoidance behavior and relief responding occurs through increased activation of the NAc and inhibition of the CeA. BLA, basolateral amygdala; CeA, central amygdala.

Figure 4: Proposed model for the dysregulation of dopaminergic circuits mediating aversive learning in addiction.

(*top right*) **Naive:** In naive animals, glutamatergic projections (*green*) from the LHb and GABAergic projections (*red*) from the RMTg modulate the activity of the VTA (Jhou et al., 2009; Lammel et al., 2012, 2014). The VTA projects to the mPFC and NAc (Morales & Margolis, 2017), and through dopaminergic signaling gates encoding of information about salient stimuli and associated cues (Phillips et al., 2003; Wanat et al., 2009). Additionally, glutamatergic neurons projecting from the BLA, hippocampus (Hipp), and PFC synapse on both D1 and D2 containing MSN populations in the NAc; Hipp inputs show stronger synaptic strength at D1 MSNs, relative to D2 MSNs, at baseline (Sjulson et al., 2018; MacAskill et al., 2014; Pascoli et al., 2014) (*bottom right*). **Chronic drug exposure:** Following chronic drug exposure, RMTg inhibitory regulation of the VTA is increased (Maroteaux and Mameli, 2012). Currently, it is unclear how projections from the LHb to VTA, and LHb to RMTg are altered by chronic drug exposure - denoted by a question mark. VTA to NAc projection (dotted) results in reduced dopamine release in the NAc both at baseline and in response to cocaine-associated stimuli (Calipari et al., 2012, Ferris et al., 2012; Willuhn et al., 2014). Basal dopamine levels in the mPFC are reduced following chronic drug exposure (Parsons et al., 1991). However, it is important to note that they are potentiated in response to drug-associated stimuli (Parsegian & See, 2014). This dysregulation of the dopaminergic system likely contributes to dysfunctional aversive learning across a number of modalities. (*left inset*) **D1 and D2 medium spiny neurons in**

the NAc: Chronic drug exposure dysregulates the encoding of these dopaminergic signals downstream via cell-type specific remodeling of MSN inputs in the NAc. D1-mediated signals are enhanced both at baseline and in response to cocaine-associated cues (Calipari et al., 2016). The enhancement of BLA and Hipp inputs to D1 MSNs, could underlie these effects (Lee et al., 2013; MacAskill et al., 2014; Pascoli et al., 2014). There is conflicting evidence in regard to mPFC inputs directly onto D1s, with a majority of reports finding reductions or no change in AMPAR/NMDAR ratios (MacAskill et al., 2014, Joffe & Grueter 2016); however, Pascoli et al., 2014 observed reductions in AMPAR/NMDAR ratios as well as increases in rectification index and EPSCs, suggesting that the input could be increased in regard to some forms of plasticity. Innervation onto D2-type MSNs by the Hipp have been reported to be enhanced (Sjulson et al., 2018), however changes in *in vivo* activity of D2-type MSNs has not been observed *in vivo* (Calipari et al., 2012). Together remodeling of this circuit in the NAc alters the activity of D1 MSNs, biasing towards D1 signaling pathways and reward-driven behaviors.