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Circuit Selectivity in Drug Versus Natural Reward Seeking Behaviors

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Abstract

Substance use disorder (SUD) is characterized, in part by behavior biased toward drug use and away from natural sources of reward (e.g. social interaction, food, sex). The neurobiological underpinnings of SUDs reveal distinct brain regions where neuronal activity is necessary for the manifestation of SUD-characteristic behaviors. Studies that specifically examine how these regions are involved in behaviors motivated by drug versus natural reward allow determinations of which regions are necessary for regulating seeking of both reward types, and appraisals of novel SUD therapies for off-target effects on behaviors motivated by natural reward. Here, we evaluate studies directly comparing regulatory roles for specific brain regions in drug versus natural reward. While it is clear that many regions drive behaviors motivated by all reward types, based on the literature reviewed we propose a set of interconnected regions that become necessary for behaviors motivated by drug, but not natural rewards. The circuitry necessary selectively for drug seeking includes an Action/Reward subcircuit, comprising nucleus accumbens, ventral pallidum, and ventral tegmental area, a Prefrontal subcircuit comprising prelimbic, infralimbic, and insular cortices, a Stress subcircuit comprising the central nucleus of the amygdala and the bed nucleus of the stria terminalis, and a Diencephalon circuit including lateral hypothalamus. Evidence was mixed for nucleus accumbens shell, insular cortex, and ventral pallidum. Studies for all other brain nuclei reviewed supported a necessary role in regulating both drug and natural reward seeking. Finally, we discuss emerging strategies to further disambiguate necessity of brain regions in drug- versus natural reward-associated behaviors.

Graphical Abstract:

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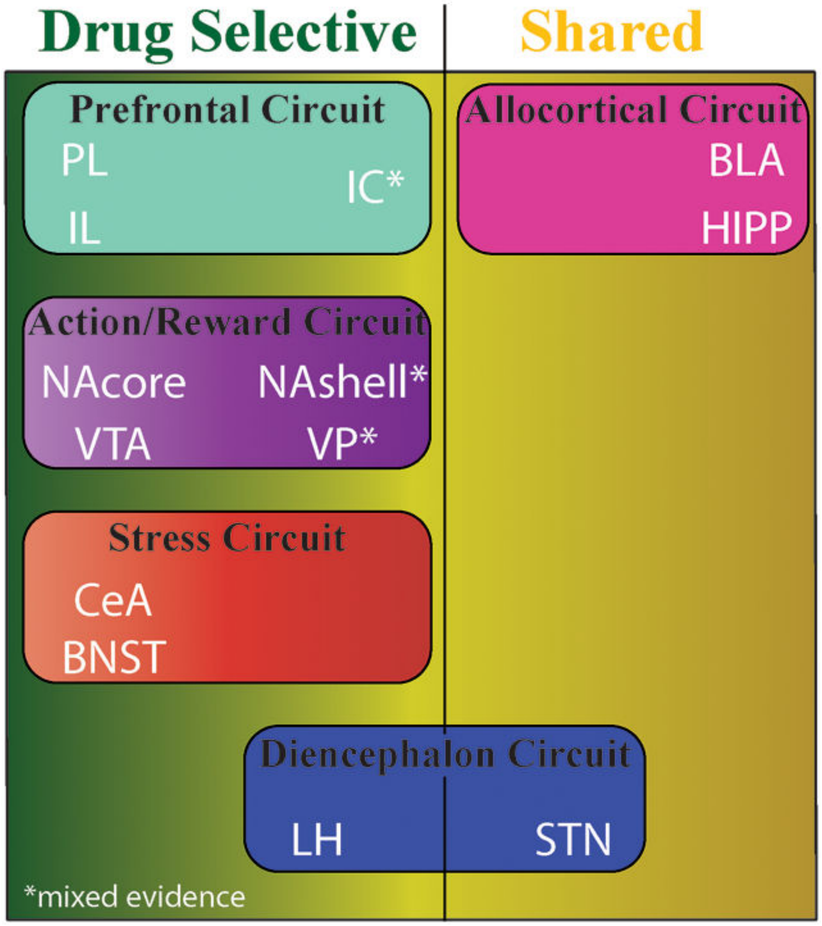

We evaluated the literature and propose circuitry necessary for drug but not natural reward seeking. Circuitry selectively necessary for drug rewards includes an Action/Reward subcircuit: nucleus accumbens core (NAcore), ventral tegmental area (VTA), Prefrontal subcircuit: prelimbic (PL), infralimbic (IL) cortices, Stress subcircuit: central nucleus of the amygdala (CeA), bed nucleus of stria terminalis (BNST), and Diencephalon subcircuit: lateral hypothalamus (LH). Evidence was mixed for nucleus accumbens shell (NAshell), insular cortex (IC), and ventral pallidum (VP). Circuitry necessary for both drug and natural reward: subthalamic nucleus (STN), basolateral amygdala (BLA), and hippocampus (HIPP). We discuss future strategies to expand this circuitry.

Keywords

Nucleus Accumbens; Drug Seeking; Natural Reward; Addiction; Reward Circuit; Stress Circuit

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Substance use disorder (SUD) is a significant and widespread burden on public and private health, incurring an estimated annual cost of $740 billion and affecting over 20 million people in the United States (Center for Behavioral Health Statistics and Quality, 2015). Pharmacological and behavioral treatments are partially effective at reducing the amount of substance used, but relapse following treatment is common. For example, the pharmacological smoking cessation aid varenicline is effective at helping smokers initiate abstinence, but the effects are transient with around 60% of smokers relapsing within 1 year of treatment (Agboola et al., 2015). Likewise, contingency management is among the most effective treatments for SUDs (Prendergast et al., 2006), however, approximately 60% of patients relapse following treatment (McLellan et al., 2000). Indeed, SUDs are characterized by a difficulty in refraining from drug use and by chronic episodes of relapse (American Psychiatric Association, 2013) induced by exposure to drug-associated cues or contexts following abstinence (Volkow et al., 2012).

Another hallmark of SUDs is the persistent procurement and consumption of abused substances at the expense of non-drug or natural sources of reinforcement (e.g. food, sex, social interaction). This tendency is reflected in several of the diagnostic criteria for SUDs: Spending considerable time obtaining the drug; Repeated failure to carry out major obligations at work, school, or home due to drug use; Stopping or reducing important social, occupational, or recreational activities due to drug use (American Psychiatric Association, 2013). Further, the fact that drug and natural rewards largely activate overlapping brain nuclei complicates research designed to disambiguate the neurobiological underpinnings of behaviors motivated by drugs and natural rewards. However, we argue here that evidence of neuronal activity in a brain nucleus or circuit is not necessarily commensurate with its necessity for reward seeking. Thus, studies showing causal relationships of particular nuclei allowed us to identify a circuit necessary selectively for behaviors motivated by drug but not natural reward. Understanding which brain subcircuits are selectively required for drug seeking, but not seeking of natural rewards, will help identify the brain sites harboring neurobiological adaptations critical for SUDs, and assist in developing selective therapies with less off-target effects on seeking of natural rewards.

Extant understanding of the neurobiological mechanisms underlying SUDs is largely based on preclinical studies using animal models. The gold standard among animal models of addiction is the drug self-administration (SA) model, in which animals first perform operant responses to earn access to drug. Subsequently, drug seeking is reduced by removing the animal from the experimental context (i.e. forced abstinence) or no longer providing access to drug upon seeking responses (i.e. extinction). After drug seeking has been reduced, animals are commonly re-exposed to drugs (i.e. primed reinstatement), drug-associated cues (i.e. cued reinstatement), drug-associated contexts (i.e. contextual reinstatement), or stress (stress-induced reinstatement) to reinitiate drug seeking behaviors (for reviews see, Crombag et al., 2008; Everitt et al., 2018; Kuhn et al., 2019; Marchant et al., 2013; Venniro et al., 2016). Increasing the duration of forced abstinence periods often increases drug seeking upon return to the experimental context (i.e. incubation of craving; Li et al., 2015). Another common model to examine drug seeking is conditioned place preference (CPP; McKendrick & Graziane, 2020), in which animals are exposed to drug in one distinct context and to vehicle or another reward in a different distinct context. Preference is indicated by time spent seeking in one or the other context when both contexts are accessible.

Investigators have identified specific adaptations and cellular activity patterns related to drug use, seeking, and refraining from seeking by manipulating and observing activity at various points in the protocols of these preclinical models (Kuhn et al., 2019). Importantly, analogous studies have been conducted where a natural reward, often sucrose, is used as the reinforcer (e.g., Bobadilla et al., 2017a; Grimm, 2020; Nair et al., 2006). However, to date it is uncommon for investigators to include both drug and natural reinforcers in the same study, and direct comparisons between these two reinforcers within the same animal are even more rare. Yet, studies that directly compare the neurobiological and behavioral effects of drug versus natural rewards are uniquely poised to clarify if observed treatment effects or adaptations and cellular activity patterns in a given region are selective for drug seeking. This rationale has likely inspired the recent increase in preclinical studies which include multiple reward modalities (see for discussion; Kuhn et al., 2019; Venniro et al., 2020).

Here we review the current body of published research that specifically examines both drug and natural reward within the same study in an effort to map the brain circuits that are necessary for seeking behaviors motivated by drug or natural reward. Because a large body of work has identified drug-specific adaptations in the nucleus accumbens (NAc) as critical for expressing seeking behaviors, we begin our analysis of the literature with studies focused on the role of the NAc in drug versus natural reward seeking. Then, we move to other brain regions that, together with the NAc, comprise the circuits driving drug and/or natural reward seeking behaviors. We recognize that different classes of addictive drugs and natural rewards may produce different neuroadaptations in given brain regions. While we make note of some of these, our primary goal is to examine whether activity in a given region is necessary for seeking. As such, we focus our review on studies that manipulate activity within each brain region. While many regions are activated by both drug and natural rewards, examining studies that manipulate activity within a given region allows the identification of regions where adaptations occur that leave those regions necessary for drug seeking, but not seeking of natural reward. We refer to these regions as “drug-selective” to indicate that while they may be involved in behaviors motivated by both drug and natural rewards, they exhibit selective plasticity and behavioral consequences in response to drugs of abuse. Table 1 provides a summary of which reports found a particular region to be selectively involved in drug-motivated behavior (i.e. drug-selective) or for both drug- and natural-reward-motivated behaviors (i.e. shared). Then, we discuss promising experimental strategies for discriminating between the neural bases of behaviors motivated by drug and natural rewards. Finally, we discuss a potential circuitry between these regions.

NAc Structure, Connectivity and Function

NAc Structure:

The NAc is a key structure of the ventral striatum that is traditionally divided into central core and surrounding shell regions (NAcore and NAshell, respectively) based on heterogeneity in structure, function, and connectivity (Scofield et al., 2016; Záborszky et al., 1985; Zahm, 1999). Most neurons within the NAc (~90–95%) are GABAergic medium spiny neurons (MSNs) that can be differentiated by expression of dopamine D1- or D2-receptor expression (Gerfen & Surmeier, 2011). Remaining neurons include interneurons expressing parvalbumin, calretinin, and choline acetyltransferase, as well as those that co-express somatostatin, neuropeptide Y, and neuronal nitric oxide synthase (Burke et al., 2017; Tepper et al., 2010). Finally, the NAc contains glia that regulate extracellular glutamate and influence synaptic plasticity (Jarvis et al., 2020; Kalivas, 2009; Kruyer & Kalivas, 2021; McGrath & Briand, 2019).

NAc Connectivity:

Connectivity differs between the NAcore and NAshell. The NAcore integrates inputs from cortical and allocortical structures involved in reward processing, goal-directed behavior to earn reward, and reinstatement (Scofield et al., 2016). The majority of NAcore inputs arise from glutamatergic afferents including the prefrontal cortex (PFC), the insular cortex (IC), the basolateral amygdala (BLA), the hippocampus (HIPP) and midline thalamus (Brog et al., 1993; Sesack et al., 1989), whereas, the ventral tegmental area (VTA), ventral pallidum (VP), and to a minor extent PFC, provide GABAergic input (Lee et al., 2014; Scofield et al., 2016). Finally, VTA and substantia nigra (SN) provide dopaminergic inputs to NAcore (Brog et al., 1993). Reciprocal projections from the NAcore innervate the SN and VP, and to a lesser extent, lateral VTA (Bernal-Gamboa et al., 2017; Groenewegen et al., 1999; Heimer et al., 1991; Tripathi et al., 2010).

The NAshell integrates inputs from a variety of brain regions central to reward learning and motivation (Castro & Bruchas, 2019). Glutamatergic afferents of the NAshell include cortical (anterior insular cortex, dorsal peduncular cortex, infralimbic cortex, orbitofrontal cortex, and prelimbic cortex) and allocortical (BLA and ventral HIPP) regions, as well as a input from the paraventricular thalamus, with quantitatively smaller glutamatergic input from the VTA (Beckstead et al., 1979; Brog et al., 1993; Mcdonald, 1991; Sesack et al., 1989). The NAshell also receives dopaminergic input from the VTA, and GABAergic inputs from the central nucleus of the amygdala (CeA), lateral hypothalamus (LH), VP, and VTA (Brog et al., 1993; Groenewegen et al., 1999). NAshell D2-MSNs project primarily to the VP, but also innervate the VTA and LH, while D1-MSNs project to the VP, VTA and LH (Gibson et al., 2018; O’Connor et al., 2015).

NAc Function:

Several functions within the NAc have direct relevance for understanding SUDs. The rewarding and reinforcing effects of different abused substances (Di Chiara & Imperato, 1988; Volkow et al., 2011c) and natural rewards (Volkow et al., 2011b; Wise, 2006) have long been associated with increased NAc dopamine release. However, individuals with SUDs often show paradoxical blunting of NAc dopamine in response to abused substances relative to nonaddicted individuals (Volkow et al., 1997, 2014) but increased NAc dopamine responses to drug-paired stimuli which correlates with drug craving (Volkow et al., 2014). This finding is supported by a study in rats where NAc lesions reduced drug SA mediated by conditioned stimuli, but had little effect on maintenance of SA without cues (Ito et al., 2004). This increased propensity for drug-paired stimuli to drive behavior has been termed incentive salience and is thought to contribute to the prepotency of drug seeking behavior (Koob & Volkow, 2016). NAc sensitivity to drug stimuli is of particular interest to SUD research due to the prominent role of drug-associated stimuli in occasioning drug craving and relapse.

NAc D2-MSNs are implicated in refraining from drug seeking (Roberts-Wolfe et al., 2018, 2019), and D2 receptor availability is reduced in individuals with SUDs (Volkow et al., 2002). Further, D2 receptor downregulation in individuals with SUDs is associated with decreased activity in cortical areas associated with decision making (Volkow et al., 2011a), and increases or decreases in D2 expression in animals results in reduced or increased sensitivity to abused substances, respectively (Bello et al., 2011; Thanos et al., 2001, 2008). These findings indicate a potential role for NAc in regulating compulsive seeking of abused substances, another hallmark symptom of SUDs.

Whether the nature of drug seeking is primarily goal-directed or habitual in individuals with SUDs is an area of growing contention. Drug seeking tends to prevail over other non-drug-related behaviors in individuals with SUDs, despite the finding that addicted individuals often describe a reduced desire to consume drugs (Berridge & Robinson, 2016). Further, drug seeking shows relative insensitivity to aversive consequences, devaluation, and reward unavailability in animal models, leading many to conclude that drug seeking becomes habitual in nature, such that drug-related stimuli drive a habitual response pattern that terminates in procuring and using drugs (Everitt & Robbins, 2016). However, a recent study indicates that drug seeking in humans tends to be highly flexible, potentially detracting from habit-based accounts of addiction (Hogarth, 2020). Regardless of the outcome of this debate, the NAc is likely to play a prominent role in the maintenance of persistent drug seeking. The NAc is involved both in habitual responding for drugs (Belin et al., 2013; Everitt et al., 2008) and in complex tasks related to outcome ambiguity or uncertainty (e.g. Mascia et al., 2019), and is thought to aid in response selection based on relative salience of inputs (Floresco, 2015). Thus, the NAc is likely involved in persistent drug-seeking behaviors regardless of whether they are described as habitual or goal-directed.

Finally, while the NAc has been shown to regulate behavior motivated by both drug and natural rewards (Kelley, 2004; Robinson & Berridge, 2000), drug-specific adaptations that occur within the NAc over the course of drug SA, extinction/abstinence, and relapse are not seen in identical sucrose SA experiments. Many studies have characterized drug-specific adaptations in pre- and post-synaptic compartments, extracellular matrix, and astroglia (i.e. the tetrapartite synapse) that lead to changes in glutamate signaling and in turn regulate drug-seeking behaviors (for detailed reviews see, Bobadilla et al., 2017b; Kruyer et al., 2020; Neuhofer & Kalivas, 2018). Taken together, existing data strongly suggest that the NAc is a critical brain nucleus for regulating the behavioral symptoms of SUDs.

Drug vs. Natural Reward in Nucleus Accumbens Core:

Drug-induced adaptations in the NAcore are necessary for the expression of seeking behaviors related to SUDs (Scofield et al., 2016). Because the NAcore is also involved in behaviors motivated by natural reward (Berridge, 2009; Salamone et al., 2003), investigations directly comparing adaptations and the effects of manipulations on drug versus natural reward in NAcore are especially beneficial for understanding how drugs, but not natural rewards lead to pathological behaviors in SUDs. Alasmari et al. (2018) found adaptations in glial glutamate regulation in the NAcore induced by ethanol and nicotine, but not sucrose. They also demonstrated that nicotine + sucrose, nicotine + ethanol, and ethanol alone decreased expression of glutamate transporter (GLT-1) and cystine glutamate antiporter (xCT) and increased expression of metabotropic glutamate receptor (mGluR1) in the NAcore relative to sucrose only or water controls. These results are consistent with the important role of the NAcore glutamate in relapse (Kalivas, 2009), as well as the role of glia in regulating glutamate in drug, but not sucrose seeking (Kruyer et al., 2020). Martin et al. (2006) found that cocaine but not food SA inhibited long-term depression in both the NAcore and NAshell after only 1 day of forced abstinence, but selectively in the NAcore after 21 days of abstinence, suggesting that adaptations specifically in the NAcore may contribute to incubation of drug craving. Moreover, Cameron and Carelli (2012) used *in vivo* electrophysiological recordings to demonstrate that neurons in the NAcore exhibited mostly reward-specific phasic activity in a multiple schedule of cocaine and sucrose reinforcement. Re-exposure to the multiple schedule after 30d of abstinence revealed that most neurons remained selectively activated, but that the percentage coding for cocaine-motivated behaviors increased, and the percentage coding for sucrose-motivated behavior decreased. Further, while the relative increase in the number of neurons coding for cocaine and decrease in neurons coding for sucrose occurred in both the NAcore and NAshell, increased cocaine coding was more dramatic in the NAcore while decreased sucrose coding was more dramatic in the NAshell. A recent study by Bobadilla et al. (2020) used a c-Fos-TRAP (Targeted Recombination in Active Populations) strategy to investigate drug-specific NAcore neuronal ensembles alongside a within-subject behavioral model in which mice were trained to self-administer cocaine and sucrose across alternating sessions. This study showed that cued reinstatement of cocaine or sucrose seeking formed NAcore ensembles that were mostly distinct, overlapping by only ~30%, and that ensembles primarily consisted of D1-expressing neurons during cued reinstatement and D2-expressing neurons during extinction. Further, while cocaine and sucrose seeking ensembles were similar in size during cued reinstatement when each reward was administered independently, mice exposed to both rewards exhibited a larger cocaine-seeking than sucrose-seeking ensemble, and the magnitude of cued reinstatement was greater for cocaine than sucrose when both cues were simultaneously available. They also noted that the size of reward-specific ensembles was significantly correlated with the magnitude of reinstated behavior. These results suggest that D1- and D2-expressing NAcore neurons encode seeking and refraining from seeking, respectively, and that mostly non-overlapping neuronal ensembles in the NAcore code for cocaine versus sucrose seeking. Finally, these data indicate that differences in recruitment to reward-specific ensembles may explain preferential relapse effects for drug compared to natural reward. Together, the studies by Alasmari et al. (2018), Bobadilla et al. (2020), Cameron and Carelli (2012), and Martin et al. (2006) suggest that drugs of abuse can lead to adaptations in the NAcore that are not shared with natural rewards, that these adaptations correspond with behavior, and that adaptations within NAc subregions may differ for drug versus natural rewards.

Consistent with the findings by Cameron and Carelli (2012), other data indicate that substances of abuse induce adaptations in the NAcore during cued reinstatement (Koya et al., 2006; Madsen et al., 2012) contextual reinstatement (Edwards et al., 2011) and CPP (Mattson & Morrell, 2005; Zombeck et al., 2008) that are not recapitulated by natural reward. Likewise, several studies show that perturbations of NAcore activity preferentially affect responding motivated by drug but not natural reward. McFarland and Kalivas (2001) found that GABA agonism within the NAcore prevented primed reinstatement of cocaine but not sucrose seeking. Spencer et al. (2014) showed that reducing excitatory transmission in NAc by inhibiting voltage-gated calcium channels attenuated primed but not cued reinstatement of cocaine seeking, and did not affect primed sucrose seeking. Sinclair et al. (2012) found that blocking NAcore glutamate receptor mGluR5 prevented cued reinstatement of alcohol but not sucrose seeking. Similarly, Peters and Kalivas (2006) showed that while mGluR2/3 antagonism reduced primed reinstatement of both cocaine and sucrose seeking, cocaine primed reinstatement was more substantially reduced than sucrose reinstatement. Czachowski (2005) showed that NAcore administration of serotonin$_{1B}$ agonist decreased ongoing alcohol seeking, but had little effect on consumption of freely-available alcohol. Conversely, a serotonin$_{1A}$ agonist decreased alcohol consumption, but not ongoing seeking. Importantly, neither agonist had an effect on sucrose consumption or seeking. Consistent with the findings of Alasmari et al. (2018) discussed above, Scofield et al. (2015) found that chemogenetic activation of NAcore glia inhibited cued reinstatement of cocaine but not sucrose seeking. Building on this data, Kruyer et al. (2019) discovered that glia were retracted from NAcore synapses following extinction of heroin but not sucrose seeking, and that cued reinstatement of heroin, but not sucrose seeking produced a transient reassociation of glia with synapses. Further, blocking glial reassociation with synapses reduced cued heroin seeking. Taken together, these results strongly indicate that the necessity of NAcore is drug selective, and support the hypothesis that the NAcore is an essential nucleus for regulating the behavioral symptomology of SUDs.

Drug vs. Natural Reward in Nucleus Accumbens Shell:

Contrary to the drug selectivity of the NAcore, studies examining the NAshell produced mixed results. Some data indicate drug selective adaptations (Crombag et al., 2005, 2008; Mattson & Morrell, 2005) and others indicate similar adaptations between drug and natural reward (Madsen et al., 2012; Zombeck et al., 2008). Manipulation studies also find mixed results, with some studies demonstrating a necessity for the NAshell in regulating behaviors motivated by drug but not natural reward. Pascoli et al. (2014) found that neurons projecting from infralimbic cortex to NAshell showed cocaine-evoked plasticity (i.e. reduced AMPA/NMDA ratio and increased rectification mediated by GluA2 lacking AMPA receptors). Optogenetic reversal of plasticity in these neurons prior to testing eliminated cue-induced reinstatement of cocaine but not sucrose seeking. Liechti et al. (2007) found downregulation of mGluR2/3 in NAshell following nicotine but not sucrose SA, and mGluR2/3 antagonism reduced ongoing nicotine but not sucrose seeking. McFarland et al. (2004) found that GABA agonism in NAshell reduced stress-primed cocaine seeking but not food-primed food seeking. However, other data indicate that the NAshell is necessary for both drug- and natural-reward-motivated behaviors. Liechti et al. (2007) reported that mGluR2/3 antagonism in the NAshell decreased cued reinstatement of both nicotine and sucrose seeking. Similarly, Guercio et al. (2015) found that deep brain stimulation of the NAshell attenuated cued reinstatement of both cocaine and sucrose seeking. Thus, the role of the NAshell in governing drug versus natural-reward motivated behaviors is not entirely clear. One potential explanation for these mixed results could be that only particular NAshell subcircuits, cell types, or neurotransmitter systems show drug selectivity. This possibility is supported by the drug selectivity of IL-NAshell (Pascoli et al., 2014) but not BLA-NAshell (Millan et al., 2017; reviewed below) projections in regulating cocaine seeking. Another potential explanation is that differences in methodology (e.g. deep brain stimulation vs. reversible inactivation, differences in behavioral paradigms) are responsible for discrepant findings.

Drug Selectivity in Circuitry in which NAc is Embedded

Prefrontal Cortex:

The prefrontal cortex is critical for decision making and executive control, and regulates reward seeking in part via glutamatergic projections to the NAc (Kalivas et al., 2005). Involvement of the PFC in SUDs is well established, where deficits associated with attribution of salience, impulsivity, motivational arousal, and self-control are accompanied by increased PFC activation by drugs or drug cues, blunted PFC activation by natural reward, and poor performance on PFC-mediated cognitive tasks (Goldstein & Volkow, 2011). Further, individuals with an extended recreational cocaine-use history but not a diagnosable SUD show increased PFC grey matter volume while individuals with cocaine use disorder show reduced PFC grey matter volume relative to non-drug-using controls (Ersche et al., 2013a). These results have led some to suggest that variations in PFC functionality may confer vulnerability or resilience to developing SUD following exposure to abused substances (Ersche et al., 2013b, 2020). Recent animal studies provide some support for this hypothesis. PFC-dependent task performance and PFC orexin receptor expression prior to beginning methamphetamine SA correlated with future methamphetamine preference (Tavakkolifard et al., 2020). Similarly, De Laat et al. (2018) found that pre-SA performance on a cognitive task and levels of PFC glutamate and glycine were associated with future rates of cocaine intake. Together these studies indicate a potential role for PFC in conferring vulnerability or resilience to the development of SUDs.

The PFC has also been described as a critical component of the final common pathway for relapse of drug seeking (Kalivas & Volkow, 2005). A serial pathway from dorsomedial PFC, to NAcore and VP is necessary for drug seeking, as perturbations of this circuit reduce seeking across different types of triggering events and drug classes (e.g. Cordie & McFadden, 2019; Doncheck et al., 2020; Hernandez et al., 2020; Ma et al., 2014; Palombo et al., 2017; Struik et al., 2019), highlighting the importance of PFC for the expression of relapse to drug seeking. Overall, these studies strongly suggest that PFC mediates pathological behaviors associated with SUDs.

Other studies have identified the role of heterogeneous regions of the prefrontal cortex in drug seeking and relapse. While a complete characterization of the role of these subregions in SUDs is beyond the scope of this review, a brief overview is provided here to aid in the discussion of drug selective effects below. PFC subregions with a notable role in SUDs and in which studies investigating drug vs natural reward exist include medial PFC prelimbic (PL) and infralimbic (IL) cortices, and the lateral prefrontal insular cortex (IC). In general, existing data implicate PL in relapse to drug seeking (Moorman et al., 2015). IL is involved in suppression of drug seeking (Peters et al., 2008), and experimentally manipulating IL activity affects relapse of drug seeking (Augur et al., 2016; Ma et al., 2014; Muller Ewald &

LaLumiere, 2018). Further, Warren et al. (2016) showed that distinct ensembles of IL neurons control food SA and extinction, and the same lab later showed that distinct ensembles regulating cocaine SA and extinction are mostly composed of IL-NAcore and IL-NAshell projection neurons, respectively. Finally, IC is thought to be involved in interoception and drug craving (Paulus & Stewart, 2014) and is strongly implicated in nicotine craving in smokers (Droutman et al., 2015; Kenny, 2011). Overall, these data suggest that heterogeneous cortical subregions are important for regulating drug-related behaviors in individuals with SUDs.

Drug selective adaptations have been noted in medial prefrontal cortex regions (mPFC; PL, IL). Koya et al. (2006) found increased immediate early gene (IEG) expression in mPFC following cued reinstatement for heroin but not sucrose relative to extinction controls. Wedzony et al. (2003) also noted increased Fos expression in mPFC following protracted abstinence from alcohol but not sucrose SA, specifically near the border of PL and IL (i.e. ventromedial PFC). In addition, Crombag et al. (2005) found increased spine density in the mPFC following amphetamine SA relative to sucrose self-administering and untreated controls. Using an innovative *in vivo* single-cell calcium imaging approach (discussed below), Siciliano et al. (2019) characterized activity patterns in neurons projecting from the mPFC to the dorsal periaqueductal grey that predicted susceptibility to compulsive alcohol drinking. These observations led the authors to optogenetically manipulate the circuit and conclude that compulsive alcohol seeking is likely driven by reduced aversion signaling. Importantly, they showed that manipulating this circuit had selective effects on alcohol but not water seeking. Because drug selective adaptations occur in several mPFC subregions, and manipulations of neurons in the mPFC affect behaviors motivated by drug but not natural reward, we will next explore the whether mPFC subregions are selectively necessary for behaviors motivated by drug but not natural rewards.

Drug vs. Natural Reward in Prelimbic Cortex: Data from PL strongly support drug selectivity. Data suggest that drug selective adaptations occur in PL during SA and extinction (Parrilla-Carrero et al., 2018), cued reinstatement (McGlinchey et al., 2016; Schmidt et al., 2005) and CPP (Mattson & Morrell, 2005). Experiments manipulating PL activity also demonstrate the necessity of PL in regulating behaviors motivated by drug but not natural reward. Schmidt et al. (2005) found that intra-PL infusions of muscimol + baclofen potentiated cued reinstatement of heroin but not sucrose seeking. Levy et al. (2007) showed that electrical stimulation in PL reduced cocaine- but not sucrose-primed reinstatement. Brown et al. (2016) reported that infusions of orexin-1 receptor antagonist into PL attenuated cued reinstatement of alcohol but not sucrose seeking. Other studies specifically implicate PL-NAcore projections in regulating drug seeking. McGlinchey et al. (2016) blocked dopamine signaling in PL and glutamate signaling in NAcore and found that inactivating this pathway attenuated cued reinstatement of cocaine but not sucrose seeking. Similarly, James et al. (2018) found that activation in PL projections innervating contralateral NAcore is correlated with cued reinstatement of cocaine but not sucrose seeking, and that blocking dopamine D1/D2 receptors in PL reduced cocaine but not sucrose seeking. Taken together, the above studies strongly indicate that PL becomes essential for drug seeking and relapse but not for behaviors motivated by natural reward.

Drug vs. Natural Reward in Infralimbic Cortex: In opposition to the drug selective response invigorating effects of the PL, the IL is largely involved in refraining from reward seeking, though the potentiation by PL and inhibition by IL is not perfectly distinguished (see, Moorman et al., 2015). While immediate early gene activity in IL is sometimes similar during drug and natural reward seeking during extinction (Schmidt et al., 2005), cued reinstatement (Schmidt et al., 2005) and CPP (Mattson & Morrell, 2005), manipulation data strongly indicate that the IL is necessary for behaviors motivated by drug but not natural reward. Van den Oever et al. (2008) showed that inhibiting endocytosis of AMPA receptor subunit GluR2 in ventromedial PFC (i.e. IL) reduced cue-induced reinstatement of heroin but not sucrose seeking. Guercio et al. (2020) found that deep brain stimulation of the IL during testing attenuated cued reinstatement of cocaine but not sucrose seeking. As discussed above, Pascoli et al. (2014) found that optogenetic reversal of plasticity in IL-NAshell neurons eliminated reinstatement of cocaine but not sucrose seeking induced by cue-exposure following forced abstinence. These findings are supported by a recent innovative study by Kane and colleagues (2020) in which rats self-administered cocaine and sucrose across alternating sessions before a 7d abstinence period. Following abstinence, rats were briefly exposed to a cued seeking task to induce Fos activation of neuronal ensembles in ventromedial PFC (i.e. IL) encoding either cocaine or sucrose. The ensembles were then selectively inactivated before a second cued reinstatement test under extinction conditions. Testing revealed that inactivation of the sucrose ensemble had no effect on cocaine or sucrose seeking, but that inactivation of the cocaine ensemble selectively attenuated cocaine seeking. Collectively, these results suggest that IL selectively regulates relapse of drug but not natural reward seeking, and that IL effects may in part be enacted by drug-encoding neuronal ensembles projecting to NAshell.

Drug vs. Natural Reward in Insular Cortex: Prior work indicates that IC is involved in drug induced devaluation of natural rewards (Moschak et al., 2018), drug craving (Naqvi et al., 2014), context-induced relapse (Arguello et al., 2017), relapse after extended withdrawal (Campbell et al., 2019), and even relapse in a novel model of contingency management (Venniro et al., 2017). The IC likely influences behavior via its projections to the NAcore (Rogers-Carter et al., 2019) and to the extended amygdala (Centanni et al., 2019; Venniro et al., 2017). Although studies examining drug versus natural rewards in IC are less common, extant data indicate that both drug and natural rewards produce IC activity (Liu et al., 2013; Tomasi et al., 2015). Some inactivation studies indicate that IC is necessary for behaviors motivated by drug but not natural reward. Hollander et al. (2008) showed that blocking orexin/hypocretin receptors with intra-IC infusions of a hypocretin receptor antagonist dose-dependently reduced responding for nicotine but not sucrose seeking under a progressive ratio schedule. Jaramillo et al. (2018) found that chemogenetically silencing IC-NAcore projections selectively decreased alcohol but not sucrose SA. Similarly, Cosme et al. (2015) found that muscimol + baclofen inactivation of dorsal anterior IC reduced cued but not primed reinstatement of cocaine seeking, an effect that was mimicked by intra-IC blockade of CRF-1 receptors, but inactivation did not influence cued, primed, or cued + primed reinstatement of food seeking. However, Haaranen et al. (2020) found that chemogenetically activating anterior IC reduced consumption of freely-available alcohol and sucrose, while inactivation had no effect. Thus some results in IC (Cosme et al., 2015; Hollander et al., 2008; Jaramillo et al., 2018) suggest IC is necessary and/or sufficient for behaviors motivated by drug but not natural rewards, and provide clues for IC involvement in specific forms of relapse and specific neurotransmitter systems. However, it is difficult to form a strong hypothesis with so few studies comparing drug versus natural reward and with the contrasting evidence by Haaranen et al. (2020). One potential explanation for these mixed findings could be that differences in experimental design (i.e. operant responding versus free consumption) or manipulation of different IC circuits (e.g. IC-NAc versus IC-hypothalamus) produced the discrepant findings. Another possibility is that these mixed findings arise from differences in IC function, as IC is involved in both interoceptive awareness of drug craving (see, Tomasi et al., 2015) and in processing salient drug events as a critical node in the salience network (e.g., Grodin et al., 2017). A recent study has defined a salience network in rats that includes projections from the ventral anterior IC to anterior cingulate cortex, as in the human salience network (Tsai et al., 2020). Further, dorsal anterior and ventral anterior portions of the IC project to the NAcore and lateral NAshell, respectively (Brog et al., 1993; Sesack et al., 1989). Thus, future work interrogating specific subregions of IC may provide more conclusive evidence regarding the necessity for IC in behaviors motivated by drug and natural reward. Collectively, these mixed data indicate that the necessity for IC in regulating behavior is mostly drug selective.

Amygdala:

The amygdala (AMY) is critical for memory-processing, emotional responses, decision making, and drug seeking via connections to the NAc and PFC (Peters et al., 2009). The amygdala has been implicated in addiction, with particular roles in negative affect during withdrawal and preoccupation with abused substances (Koob & Volkow, 2016). Indeed, simultaneous downregulation of PFC and increased activity in AMY likely confer vulnerability and contribute to negative affect and relapse (Ruisoto & Contador, 2019). Like NAc and PFC, activity in AMY is increased when individuals with SUDs are exposed to cues related to abused substances (Jasinska et al., 2014) and resting state functional connectivity is increased in chronic heroin users relative to non-using controls (Ma et al., 2009). Finally, a review of neuroimaging studies by Mihov and Hurlemann (2012) revealed consistent increases in AMY activity during abstinence from nicotine, greater reactivity to nicotine-paired cues than neutral cues, reduced AMY activation by harm signals, and increased AMY activity during relapse prevention therapy in smokers. These findings led the authors to suggest nicotine cue-reactivity and decreased sensitivity to harm-signals as potential vulnerability biomarkers for smoking relapse. Taken together, the studies above suggest that AMY plays a central role in the pathological behaviors associated with SUDs, with particular involvement in stress and emotional processing. Importantly, these effects are mediated by different subregions within AMY, with components of the extended amygdala (i.e. central nucleus of the amygdala [CeA], bed nucleus of the stria terminalis [BNST]) controlling negative affect and stress reactivity (Centanni et al., 2019), and the basolateral amygdala mediating cue reactivity (See et al., 2003) and reward valuation (Wassum & Izquierdo, 2015). Thus, we will explore the necessity of these subregions for regulating behaviors motivated by drug and natural reward next.

Drug vs. Natural Reward in the Central Nucleus of the Amygdala: Subregions in AMY differ with respect to drug selectivity. The central nucleus of the amygdala (CeA) is implicated in threat detection, regulation of mood and affect, reward valence, and is critically involved in behavioral symptoms of SUDs (Centanni et al., 2019). Studies also strongly indicate drug selectivity in CeA, and CeA Fos activation is increased following cued reinstatement of drug but not natural-reward seeking (Madsen et al., 2012). Walker et al. (2020) reported that blocking CART (cocaine and amphetamine regulated transcript) signaling via antibody infusions into CeA attenuated stress-induced reinstatement of alcohol but not sucrose seeking. Yang et al. (2009) found that normalizing reduced levels of substance P in CeA of alcohol preferring rats (relative to non-preferring rats) reduced ongoing SA of alcohol but not sucrose, suggesting a specific role for CeA substance P signaling in alcohol-motivated behaviors. Similarly, Anderson et al. (2019) found that systemic and intra-CeA administration of a kappa opioid agonist increased and intra-CeA antagonist administration decreased binge like alcohol consumption, but systemic administration of neither drug affected sucrose consumption in the same model. McFarland et al. (2004) showed that GABA agonism in CeA resulted in reductions in stress-induced reinstatement of cocaine seeking, but not primed reinstatement of food seeking. Simms et al. (2012) found that intra-CeA infusions of glucocorticoid antagonist selectively attenuated stress-induced reinstatement of alcohol, but not sucrose seeking, suggesting a specific role for CeA in mediating stress-induced reinstatement of drug seeking. Cain, Denehy, and Bardo (2008) classified rats as high or low responders (HR & LR, respectively) based on activity in an inescapable novel environment, a task related to sensation seeking which is positively correlated with substance use in humans. They found that intra-CeA infusion of $GABA_A$ agonist reduced amphetamine seeking only in HR rats, while sucrose seeking was not differentially affected between HR and LR rats. Thus, CeA appears to be integral in expression of high-rate drug seeking in high-sensation seeking animals. Altogether, these results strongly suggest that CeA in necessary selectively for drug-related behaviors.

Drug vs. Natural Reward in the Bed Nucleus of the Stria Terminalis: CeA is densely interconnected with the bed nucleus of stria terminalis (BNST), and this connection is implicated in several behaviors associated with SUDs, including drug intake, escalation of drug use, and relapse (Centanni et al., 2019). BNST plays a major role in aversive learning and memory, and serves as an interface between reward and aversion systems by integrating inputs including PFC and AMY with outputs to brainstem regions governing response to harm signals and to the VTA, a key node for the mesocorticolimbic reward pathway (Stamatakis et al., 2014). Due to its role in regulating both aversion and reward, the BNST is likely to be critically involved in the neural circuits that underlie SUD. Accordingly, studies comparing the role of BNST in regulating behaviors motivated by drug and natural reward find drug selectivity. Studies have described drug selective adaptations in BNST (Lee et al., 2015; Shalev et al., 2001), and BNST manipulations produce drug selective results. Companion and Thiele (2018) found that silencing BNST to VTA projections disrupted ongoing alcohol but not sucrose drinking. Krawczyk et al. (2013) found that D1-receptor-mediated long term potentiation (LTP) of $GABA_A$ in the oval region of the lateral BNST (ovBNST) was associated with prolonged SA of cocaine but not sucrose. Further, blocking this effect with intra-ovBNST infusions of a D1 antagonist reduced progressive ratio breakpoints for cocaine but had no effect of breakpoints for sucrose. These results indicate a role for D1-mediated LTP in ovBNST in regulating enhanced motivation for drug rewards in SUDs. Pleil et al. (2015) found a role for BNST neuropeptide Y receptors in controlling binge drinking of alcohol but not sucrose. Using a drinking in the dark paradigm, they found that agonism of Y1R in BNST reduced alcohol drinking and Y1R antagonism increased alcohol drinking. Importantly, neither manipulation affected sucrose drinking in the same paradigm. Further, they isolated this effect to CRF neurons, suggesting a drug selective role for neuropeptide Y signaling in BNST CRF neurons. Thus, evidence supports drug selectivity in BNST, with a particular emphasis on affect-related behaviors.

Drug vs. Natural Reward in Basolateral Amygdala: BLA is an allocortical region thought to integrate stimulus sensory information and affective valence, encode various aspects of reward, including history, value, and cost, and influence behavioral symptoms of SUDs by mediating habit and drug-induced changes in reward valuation (Wassum & Izquierdo, 2015). Evidence indicates that BLA is involved in behaviors motivated by both drug and natural reward, with studies revealing increased BLA activity following cued reinstatement (Koya et al., 2006; Madsen et al., 2012) and CPP expression (Mattson & Morrell, 2005) of both drug and natural reward. BLA manipulations also mostly produce effects on both drug- and natural-reward motivated responding. Guercio et al. (2015) showed that deep brain stimulation in BLA reduced primed reinstatement of both cocaine and sucrose seeking. Similarly, Milla, Kim, and Janak (2017) found that optogenetic activation of BLA neurons projecting to NAshell similarly reduced cued reinstatement of alcohol and sucrose seeking. However, Sinclair et al. (2012) found that intra-BLA blockade of mGluR5 eliminated cued reinstatement of alcohol but not sucrose seeking. Thus, future studies will need to carefully compare behaviors motivated by drug and natural rewards across experimental phases to determine if drug selective effects occur in BLA. At present, extant data suggest that BLA has a common role in regulating behavior motivated by both drug and natural reward.

Hippocampus.

The hippocampus (HIPP) is heavily implicated in learning and memory and sends glutamatergic projections to NAshell (ventral HIPP), and to a lesser extent to NAcore (dorsal HIPP; Britt et al., 2012; Groenewegen et al., 1987; Kelley & Domesick, 1982). HIPP is also involved in SUDs, where increased activity is associated with the formation of salient drug-stimulus associations and decreased activity is associated with drug withdrawal, potentially contributing to relapse (Kutlu & Gould, 2016). In addition, several classes of abused substances can affect neurogenesis in HIPP, which is thought to contribute to inflexible decision making, negative affect, and relapse in SUDs (Canales, 2012). Indeed, blocking neurogenesis in HIPP increased cocaine SA and cued reinstatement in mice (Deroche-Gamonet et al., 2019). A recent review emphasized the role of HIPP in stress-, context-, and cue-induced relapse, and suggested that HIPP may regulate drug SA and relapse via inputs to PFC (Goode & Maren, 2019). In addition, ventral HIPP projections to NAshell regulate cocaine seeking after abstinence (Pascoli et al., 2014). Overall, these findings indicate that HIPP plays an important role in the behavioral symptomology of SUDs.

Drug vs. Natural Reward in the Hippocampus: Despite the role in regulating substance use and seeking discussed above, most studies reveal that the HIPP function is necessary for both drug and natural reward seeking. Data indicate both drug selective (Alasmari et al., 2018; De Laat et al., 2018) and shared adaptations (Crombag et al., 2005; Madsen et al., 2012) in HIPP, and manipulating neuronal activity in HIPP reveals involvement in both drug and sucrose seeking. Guercio et al. (2020) found that deep brain stimulation in HIPP reduced primed-reinstatement of both cocaine and sucrose seeking. Alternatively, Noonan et al. (2010) used irradiation to suppress HIPP neurogenesis and observed increased SA, progressive ratio breakpoints, resistance to extinction, and context-induced reinstatement in cocaine versus sucrose self-administering animals. The mixed outcomes of these studies suggest future work is needed to confidently determine whether drug selective effects occur in HIPP. Further, manipulation studies specifically investigating distinct HIPP subregions and projections could be beneficial for understanding how HIPP contributes to behaviors motivated by drug and natural reward. Together, these data indicate that necessity of HIPP is shared between behaviors motivated by drug and natural rewards.

Ventral Tegmental Area:

The ventral tegmental area (VTA) is the major source of mesocorticolimbic dopamine, is critical for reward processing, motivational salience, and learning, and sends inputs to the NAc (Russo & Nestler, 2013). The role of VTA in drug- (Lüscher & Malenka, 2011) and natural-reward-motivated behavior (Morales & Margolis, 2017) is well established, and abused substances modulate both excitatory and inhibitory effects within VTA (Oliva & Wanat, 2016). In humans, Gu et al. (2011) showed that VTA resting state functional connectivity was reduced in cocaine users relative to healthy controls, and notably VTA connectivity to NAc was reduced. While these results indicate a role for VTA in SUDs, it is important to assess drug selectivity of VTA due to its known involvement in mediating behavior motivated by natural reward.

Drug vs. Natural Reward in the Ventral Tegmental Area: Existing reports largely indicate drug selectivity in VTA. Data indicate that adaptations in VTA are drug selective (Wang et al., 2012), as are the effects of VTA manipulations. Rinker et al. (2017) showed that intra-VTA antagonism of CRF-1 and activation of CRF-2 receptors attenuated binge-like drinking of alcohol but not sucrose. Further, chemogenetic inhibition of BNST-VTA projecting neurons expressing CRF selectively reduced alcohol seeking. Czachowski et al. (2012) demonstrated that while tetrodotoxin inactivation of VTA decreased seeking of both alcohol and sucrose, intra-VTA glutamate antagonism selectively reduced alcohol seeking at high doses, demonstrating a reward- and dose-dependent effect. Further, neither manipulation affected consumption of either reward, indicating a specific role for VTA glutamate in regulating motivation to seek alcohol. Relatedly, Sun et al. (2005) found that blocking VTA glutamate receptors attenuated primed reinstatement of cocaine but not sucrose seeking. In addition, several other studies have shown drug selective effects of VTA on relapse. Solecki et al. (2019) found that optogenetic inhibition of VTA dopamine neurons reduced cued reinstatement of cocaine but not food seeking. Addy et al. (2018) found that intra-VTA infusions of calcium channel blocker selectively attenuated cue-induced cocaine-seeking, without altering cocaine reinforcement nor cue-induced sucrose-seeking. Solecki et al. (2018) showed that VTA noradrenergic signaling selectively regulates cued cocaine seeking, as evidenced by decreases in cued reinstatement of cocaine but not sucrose seeking following intra-VTA infusions of α1 and α2 antagonists. Brown et al. (2018) demonstrated a drug selective role for inflammatory signaling in VTA on relapse by blocking inflammatory signaling in VTA, which reduced primed reinstatement of cocaine but not sucrose seeking. Finally, preventing the dopaminylation of histone H3 in the VTA prevents reinstatement of cocaine but not food seeking following re-exposure to cues after extended forced abstinence (Lepack et al., 2020). In sum, extant literature strongly suggests that VTA shows drug selectivity during SA and relapse.

Diencephalon (thalamus and hypothalamus):

The thalamus mediates cognitive function as well as goal-directed and motor behaviors via projections to the PFC and striatum which also establish a role for the thalamus in reward circuitry (Huang et al., 2018). A recent review by Huang et al. (2018) highlights several adaptations in the thalamus of individuals with SUDs. First, grey matter is reduced and this reduction is correlated with drug craving, length of substance use, time in abstinence, and relapse. Differences in thalamic activity were observed with a variety of methods, and differences in functional connectivity were noted between the thalamus and other regions discussed here, including AMY, NAc and PFC. Thalamic activity was reduced in response inhibition tasks, and this decrease was correlated with SUD severity. Finally, thalamic activity was increased in response to drug-paired stimuli in individuals with SUDs relative to healthy controls.

The hypothalamus also plays an important role in regulating behaviors characteristic of SUDs. Orexin/hypocretin is a neuropeptide originating the lateral hypothalamus (LH) and orexin has been shown to play an important role in highly-motivated responding (including for drugs) and in negative affect, stress, and anxiety (Hopf, 2020). Interestingly, orexin neurons appear to be activated preferentially by cocaine but not highly palatable food in one study (Matzeu & Martin-Fardon, 2018), but other studies find mixed evidence for activation of orexin neurons by natural reward (for discussion see, Hopf, 2020). Finally, Orisni et al. (2018) reported that increased functional connectivity during early abstinence from cocaine vs. sucrose seeking in rats varied with respect to subregions of the thalamus and hypothalamus. Thus, regions within the diencephalon appear to play a role in characteristic behaviors of SUDs. We explore drug selectivity in some of these regions of the diencephalon next.

Drug vs. Natural Reward in Diencephalon: The lateral hypothalamus (LH) is involved in modulating motivation, reward, and satiety, and projects to nodes in the mesocorticolimbic reward pathway (Castro et al., 2015). The studies that have directly compared drug and natural reward in LH find drug selectivity. While Fos activation is similar following cued reinstatement of drug and natural rewards (Madsen et al., 2012), manipulation studies in LH suggest selective involvement in drug-motivated behaviors. Levy et al. (2007) showed that deep brain stimulation in LH reduced cued reinstatement of cocaine but not sucrose seeking. Similarly, Marchant et al. (2009) found that inactivation of LH with muscimol + baclofen reduced contextual reinstatement of alcoholic beer seeking, but not sucrose seeking. Moreover, they found evidence indicating that these effects were likely dependent on projections to NAshell. Perineuronal nets in the dorsal zone of the LH are necessary for cocaine, but not food CPP, cocaine, but not food SA, and cue-induced reinstatement of cocaine but not sucrose seeking (Blacktop et al., 2017; Blacktop & Sorg, 2019). In addition, the LH derived neuropeptide orexin has been shown to potently reduce alcohol but not sucrose drinking (Lopez et al., 2016), and orexin is necessary for cocaine but not sucrose SA in sated rats (España et al., 2010). Thus, extant studies strongly indicate drug selectivity within LH, with a particular role for LH-derived orexin in controlling drug motivated responding.

The subthalamic nucleus (STN) is implicated in cognition, motivation, and emotion and regulates motor action via connections with ventral pallidum, substantia nigra and globus pallidus via the canonical indirect pathway, and via direct cortical inputs (i.e. the hyperdirect pathway; Bonnevie & Zaghloul, 2019). STN also shows interesting effects with respect to addiction, in that it bidirectionally controls motivated seeking of drug versus natural reward (Hamani et al., 2017). Baunez et al. (2005) found no effect of lesions in STN when each cocaine or sucrose response was reinforced (i.e. fixed ratio 1 schedule). However, STN lesions increased responding for sucrose and decreased responding for cocaine under progressive ratio conditions. They also found that STN lesioned animals increased preference for a food-paired compartment and decreased preference for a cocaine-paired compartment (relative to non-rewarded compartments) in a CPP assay. Similarly, Rouaud et al. (2010) found that deep brain stimulation in STN increased place preference and progressive ratio breakpoints in sucrose-seeking animals, and decreased place preference and progressive ratio breakpoints in cocaine-seeking animals. Further, they showed that STN deep brain stimulation reduced compensatory increases in cocaine seeking following decreasing doses relative to non-stimulated controls. While these data excitingly suggest that STN bidirectionally controls responding motivated by drug vs. natural reward, they also indicate a role for STN in regulating behaviors motivated by both drug and natural reward. As such, these data indicate a shared role for STN in regulating behaviors motivated by both drug and natural reward.

Ventral Pallidum:

The ventral pallidum (VP) has reciprocal connections with NAc and VTA and sends outputs directly to the thalamus (Smith et al., 2009). VP is implicated in both hedonic “liking” and incentive motivational “wanting” of reward (Smith et al., 2009), as well as drug seeking, stimulus discrimination, working memory, and relapse (Root et al., 2015). Thus, VP is an important nucleus in regulating behaviors motivated by both drug and natural reward. Heinsbroek et al. (2020) reported that specific cell types in VP are involved in refraining from drug seeking and cued reinstatement. Specifically, *in vivo* single-cell calcium imaging of VP glutamate neurons revealed the highest activity during extinction, and chemogenetic stimulation of these neurons attenuated cued reinstatement of cocaine seeking. VP GABA and enkephalin neurons were most active during cued reinstatement, and chemogenetic stimulation of these neurons reinstated cocaine seeking. Similarly, Creed et al. (2016) showed that VP synapses from NAc D1-neurons were potentiated while synapses from NAc D2-neurons were depressed following cocaine exposure. Further, they found that reversing potentiation of NAc D1-neuron synapses in VP reduced cocaine sensitization, and reversal of depression in NAc D2-neuron synapses in VP increased motivation and decreased negative affective responses to natural reward (i.e. orofacial responses to sucrose). Together, these studies establish that VP is critically involved in mediating behavioral symptoms of SUDs.

Drug vs. Natural Reward in the Ventral Pallidum: Evaluations comparing the effects of VP manipulations on drug versus natural reward are mixed, but mostly show drug selectivity. Li et al. (2009) found that systemic, intra-VP, or intra-NAc infusion of mGluR7 agonist AMN082 reduced cocaine seeking while systemic infusions had no effect on sucrose seeking. Further, they showed that pre-treatment with AMN082 blocked cocaine-induced decreases in extracellular GABA concentrations in VP. Intra-VP or intra-NAc infusions of mGluR7 antagonist MMPIP blocked the effect of AMN082, leading the authors to conclude that mGluR7s in the NAc-VP GABAergic pathway are involved in selectively mediating ongoing cocaine seeking. Similarly, Heinsbroek et al. (2017) found that chemogenetic stimulation of D1-MSNs in NAcore potentiated cued reinstatement of cocaine but not sucrose seeking. Though this manipulation occurred in NAc, they showed that simultaneous chemogenetic stimulation of NAc D1-MSNs and inhibition of VP reversed potentiation of cued reinstatement, indicating that the effect was dependent on D1 NAc-VP projections. June et al. (2003) found that infusing a $GABA_{A1}$-receptor-specific ligand into the VP selectively reduced alcohol but not sucrose seeking in two alcohol preferring rat strains. However, McFarland and Kalivas (2001) found that injections of GABA agonists muscimol + baclofen into VP reduced primed reinstatement of both cocaine and food seeking. Together, these studies mostly suggest that VP, and particularly the NAc-VP pathway show drug selectivity. However, it is difficult to confidently assert that VP shows drug selectivity with so few studies, and some contrary evidence. One potential explanation for these divergent findings lies in the methodology. McFarland and Kalivas (2001) assessed primed reinstatement, while Heinsbroek et al. (2017) examined cued reinstatement. Because VP is known to regulate hedonic responses to abused substances, it is possible that deactivating VP reduced the perceived value of both cocaine and sucrose, thereby blunting priming-induced reinstatement. VP is also a heterogeneous structure, consisting of distinct subregions, and containing different cell types and output pathways to AMY, LH, NAc, STN, PFC, VTA, diencephalon, and brain stem (see, Prasad et al., 2020; Root et al., 2015). Thus, another hypothesis is that manipulations in different subregions within VP may influence different output pathways, and there is some support for differential roles of VP output pathways (Prasad et al., 2020) and cell types (Heinsbroek et al., 2020) in regulating drug-motivated behavior. Regardless of the reason for these mixed results, the NAcore-VP pathway appears to mostly show drug selectivity.

Limitations and Promising Technology for Future Studies

Limitations:

One limitation of the current review is that the extant studies examined only comparisons between drug reward and non-pathological behaviors motivated by natural reward. A growing literature is directed at understanding the similarities and differences in neurobiological factors contributing to so-called behavioral addictions (e.g. gambling disorders, eating disorders, exercise addiction) and SUDs (e.g., Chamberlain et al., 2016; Hadad & Knackstedt, 2014; James & Tunney, 2017). While recent discussions have drawn parallels between the characteristic behaviors and neurobiological mechanisms of both pathologies (e.g., Fletcher & Kenny, 2018; Kuhn et al., 2019), studies employing protocols for directly comparing pathological natural and drug reward seeking do not yet exist.

An obvious limitation is that there exist relatively few studies directly comparing the necessity of a brain nucleus or circuit in drug and natural reward. Below we outline behavioral paradigms that will facilitate this comparison in future studies. The vast majority of the work we discuss compared reinstated seeking of a drug (most often cocaine) in one group versus sucrose in another group and employed relatively broad manipulation techniques to assess the necessity of the specified region for controlling behavior. Thus, future studies utilizing more finely-grained analyses are needed to refine the proposed drug selective circuitry we compile in Figure 1C. In the following sections, we discuss promising protocols and technologies that will allow investigators to draw more nuanced conclusions regarding the role of brain circuits in regulating drug versus natural reward seeking.

Behavioral Models:

Polysubstance use is highly prevalent among people suffering from substance use disorders (Crummy et al., 2020; Liu et al., 2018). The rise of the opioid epidemic in the United States has indeed precipitated polydrug-induced overdoses, notably due to the use of opiates as drug-cutting ingredients (Meier et al., 2020; Nolan et al., 2019). Besides polysubstance abuse, humans have complex lives comprising many sources of non-drug rewards, such as food, water, social interaction, or sex. Like drugs, these rewards drive and influence behavior constantly. It is therefore important for future studies to determine how the simultaneous use of multiple drugs or competing rewards affects the brain. Mounting evidence indicates that chronic exposure to unmixed drugs of abuse induces drug selective effects that may occur only at particular stages of addiction (e.g., Cameron & Carelli, 2012; De Laat et al., 2018; Yager et al., 2019), in particular modalities of relapse (e.g., Spencer et al., 2014; Wunsch et al., 2017), or in particular subsets of subjects (e.g., Cain et al., 2008; Hernandez & Moorman, 2020). Thus, strategies that allow for drug:drug and drug:natural-reward comparisons in the same animal across experimental phases will shed light on how individual differences and drug-induced adaptations in neurobiology selectively regulate drug reward, drug seeking, and refraining from drug seeking. Making comparisons between drugs of different classes or drugs and natural rewards in animal models can be challenging due to differences in routes of administration (e.g. oral versus intravenous), onset of action (e.g. quick for cocaine, slow for alcohol), and direct effects different rewards on behavior (e.g. increased activity by stimulants and decreased activity by depressants). However, these difficulties can be minimized with careful arrangement of experimental paradigms and validation of interesting findings in more societally-relevant paradigms. Indeed, any interesting findings with the potential to further understanding of the neurobiological underpinnings of SUDs or contribute to the development of novel therapies should be validated using procedures high in face validity.

To increase the face validity of animal models of SUDs, preclinical models designed to investigate specific endophenotypes underlying SUDs have recently emerged, including drug-induced alterations in motivation for natural reward (e.g., Creed et al., 2016; Hart et al., 2018), relapse following analogues of human behavioral interventions using natural rewards (e.g., Nall et al., 2018; Venniro et al., 2019), and resistance to aversive effects of drugs (e.g., Marchant et al., 2019; Nall & Shahan, 2020). However, there is currently little work directly comparing drug versus natural reward using these preclinical models. Thus, while polyreward models are more complex than non-mixed reward paradigms, they more closely approximate key features of SUDs in humans. Future work using these behavioral models along with the finely-grained biological assays discussed below could be fruitful for determining how drugs of abuse, but not natural reward, lead to pathological behaviors indicative of SUDs.

Cellular Ensembles and Subpopulations:

The majority of the studies discussed in this review compared natural reward with drug reward for purposes of controlling for effects mediated by the behavioral protocol. However, it is becoming increasingly apparent that groups of neurons (i.e. neuronal ensembles) within the same brain nucleus of an animal may encode both drug and natural rewards, while other ensembles may selectively motivate responding for one or another reward (Bobadilla et al., 2020; Cameron & Carelli, 2012; Carelli et al., 2000; Cruz et al., 2013; DeNardo & Luo, 2017; Kane et al., 2020; Pfarr et al., 2018). While some studies indicate a relatively small overlap in drug and natural-reward ensembles (e.g., Bobadilla et al., 2020; Cameron & Carelli, 2012), others indicate larger overlap (e.g., Pfarr et al., 2018). Ensembles may also differentially code behaviors related to SA and refraining from seeking during extinction. Indeed, there is evidence that self-administration and extinction of both cocaine (Warren et al., 2019) and food seeking (Warren et al., 2016) depend, in part, on mostly independent ensembles of IL neurons. Further, cocaine SA and extinction ensembles are composed primarily of IL-NAcore and IL-NAshell projection neurons, respectively (Warren et al., 2019). As such, comparisons of individual neuron activity within-subject could provide particularly precise data regarding drug selectivity and differential control over drug-related behaviors. Further, a variety of approaches, such as TRAP (DeNardo et al., 2019) or Calcium Modulated Photoactivatable Ratiometric Integrator (CaMPARI; Moeyaert et al., 2018) strategies have been developed that allow these neuronal ensembles to be tagged and manipulated *in vivo*, providing rich data on how specific cellular ensembles control motivated behavior (for discussion see, Cruz et al., 2013; Whitaker & Hope, 2018).

Individual cell types can also differentially control behavior. For example, a growing body of evidence indicates differential roles for D1- and D2-MSNs in NAcore in regulating behavior, with specific D1-MSN circuits mostly promoting drug seeking and D2-MSN circuits mostly inhibiting seeking (e.g., Bock et al., 2013; Gibson et al., 2018; Heinsbroek et al., 2017; Kravitz et al., 2012; Lobo & Nestler, 2011; Roberts-Wolfe et al., 2018). The dual-reward study discussed above by Bobadilla and colleagues (2020) revealed that reward- seeking ensembles were mostly comprised of D1-MSNs within NAcore during seeking, and mostly D2-MSNs during extinction, showing that opposing control over behavior by NAcore D1- and D2-MSNs is also recapitulated in recruitment of those cell types to specific cellular ensembles. Recent evidence also indicates that individual cell types in VP differentially control behavior. As detailed above, Heinsbroek et al (2020) used a calcium imaging approach to demonstrate that activity in glutamatergic VP cells was high while activity in GABAergic or an enkephalin-expressing subpopulation of GABAergic VP cells was low during extinguished cocaine seeking. Chemogenetic stimulation of VP glutamate cells attenuated extinguished cocaine seeking, while stimulation of VP GABA and enkephalin cells reinstated cocaine seeking. Importantly, recent follow-up experiments showed that while activation of VP glutamate cells also inhibited sucrose seeking, activation of enkephalin neurons did not augment sucrose seeking and activating GABA neurons produced mixed results on sucrose seeking (Figure 1A). These data also highlight the power of the relatively new *in vivo* single-cell calcium imaging approach, that can provide information on cellular activity in real time across different phases of drug-seeking (see also, Siciliano & Tye, 2019). Further, calcium imaging allows for tracking cells over time, and clustering of individual cells into ensembles based on similar patterns of calcium activity. Such analyses can provide rich within-subject data regarding changes in ensemble activity across experimental phases and in response to both drug and natural reward. Together, the studies discussed in this section indicate the utility of studying drug selective and nonselective involvement of brain circuits in neuronal subpopulations within each nucleus or in subpopulations that have distinct axon terminal fields or unique activity patterns. Ideally, these more nuanced analyses would be utilized in conjunction with a within-subjects protocol (see above) to directly compare behaviors motivated by drug and natural rewards across experimental phases.

Discussion

SUDs are characterized, in part, by biased behavior toward substances of abuse and away from natural rewards, as reflected by many of the symptoms/diagnostic criteria of SUDs. Studies that examine the effects of drug versus natural reward within brain nuclei provide insight on where addictive drugs might produce neuroadaptations that facilitate drug seeking without altering natural reward seeking, a potentially critical distinction in developing therapies to selectively target drug seeking. The studies reviewed here examined the role of NAc and the circuitry in which NAc is embedded in governing behaviors motivated by drug versus natural rewards. Table 1 provides a summary of studies that found specific regions to be necessary selectively for drug-motivated behaviors (i.e. drug selective) or for both drug and natural reward motivated behaviors (i.e. shared). Based on the reviewed studies that examined drug selectivity we characterized the role of each region as drug selective or shared between natural and drug reward (Figure 1B), and then clustered nuclei into larger functional groups for discussion purposes (Figure 1C).

Manipulations in the NAcore, PL, IL, LH, VTA, CeA and BNST selectively altered drug- but not natural-reward motivated behavior (i.e. the Motivation to Action Circuit, Figure 1C). Drug selective necessity of the NAcore and VTA (i.e. Action/Reward subcircuit) as well as PL and IL is perhaps unsurprising, as these many of these regions are major components in the mesocorticolimbic reward pathway (Cooper et al., 2017), which is heavily implicated in behavioral symptomology of SUDs. Indeed nodes in this circuit are responsible for increased salience of drug cues and reward (Berridge & Robinson, 2016). Moreover, the PL and IL (i.e. Prefrontal subcircuit) were selectively necessary in drug seeking, as another of the major pathologies of SUDs is altered executive functioning, which is characterized by behavioral symptoms such as impulsivity (Jupp & Dalley, 2014) and drug-biased decision making (Paulus, 2007), and driven by regions in the Prefrontal subcircuit (Goldstein & Volkow, 2011). Further, interplay between the Action/Reward and Prefrontal subcircuits is carried out by glutamatergic PL-NAcore and dopaminergic VTA-NAcore circuits and critical for behavioral symptoms of SUDs (e.g., Shen et al., 2014). Drug selectivity in CeA and BNST (i.e. Stress subcircuit) is also predictable given the role of the extended amygdala in controlling the negative, stressful aspects of SUDs, including negative affect, blunting of natural reward, and withdrawal (Centanni et al., 2019). Finally, drug selective necessity of LH is consistent with recent literature suggesting that orexin/hypocretin neurons originating in LH and projecting widely across cortical and allocortical structures (i.e. Diencephalon subcircuit) play an important role in many of the behavioral symptoms of SUDs including enhanced motivation for abused substances, stress/anxiety, and compulsive drug seeking (Hopf, 2020). We certainly recognize that each subcircuit could be further parsed into functionally independent subcircuits. For example, the Action/Reward subcircuit contains NAcore and NAshell, which are well documented to serve different functions in several paradigms(Bossert et al., 2007; Cartoni et al., 2016; Di Chiara, 2002; Floresco et al., 2008). However, future research is needed to develop more nuanced understanding of the role of these interconnected regions in controlling behaviors motivated by drug versus natural reward. Altogether, the drug selectivity of nuclei within these subregions is likely to govern many of the behavioral symptoms of SUDs.

Data from other regions canonically thought to respond to abused substances and regulate SUD-associated behaviors indicated a shared necessity for regulating behaviors motivated by both drug and natural reward. These included BLA, HIPP, and STN (i.e. Reward Conditioning circuit). The shared involvement of the BLA and HIPP (i.e. Allocortical subcircuit) can be predicted based on their critical roles in fundamental learning processes necessary for mammals to learn and recall associations between rewards and environmental stimuli. Thus, inactivation of these regions eliminates recall of discrete or contextual information associated with either drug or natural rewards (Cador et al., 1989; Fuchs et al., 2005; Grimm & See, 2000; Riaz et al., 2017; Rogers & See, 2007; Stefanik & Kalivas, 2013). The STN (part of the Diencephalon subcircuit) is well established as a primary output within the extrapyramidal motor system and densely innervated by the globus pallidus and ventral pallidum (e.g., Root et al., 2015; Shink et al., 1996; Tillage et al., 2020). As an integral component of motor behavior, it is perhaps not surprising that STN is needed to execute behaviors motivated by both natural and drug reward. However, it is worth highlighting that the unique bi-directional enhancement of natural-reward motivated behaviors and diminution of drug-motivated behaviors in STN does provide a potential avenue for future SUD therapies (e.g., Pelloux & Baunez, 2013; Wang et al., 2018). Overall, regions of the Reward Conditioning circuit are critically involved in both drug and natural-reward motivated behaviors.

Mixed-involvement was found for three regions: NAshell, IC, and VP. NAshell integrates a variety of cortical and allocortical inputs with varying levels of drug selectivity. For instance, the IL-NAshell projection showed drug selectivity (Pascoli et al., 2014) but the BLA-

NAshell pathway did not (Millan et al., 2017). Further, mostly individual cellular ensembles within NAshell code for drug and natural reward (e.g. Cameron & Carelli, 2012). Thus, it is likely that the mixed data in NAshell arise from differential connectivity or effects on specific cell types/ensembles. IC and VP are heterogeneous structures, but little animal research has simultaneously compared the role of subregions in IC and VP on behaviors motivated by drug and natural reward. Indeed, the dorsal anterior and ventral anterior portions of the IC project to the NAcore and lateral aspect of NAshell, respectively (Brog et al., 1993; Sesack et al., 1989). Given that NAcore showed drug selectivity, but NAshell data were mixed, it is worth investigating drug selectivity within these specific IC-NAc projections. Similarly, VP subregions also have different projection targets (e.g., Groenewegen et al., 1993). Ventromedial VP projects to both VTA and LH, regions that showed drug selectivity. By contrast, dorsolateral VP projects to STN, which did not show drug selectivity in the studies reviewed here. Finally, cell types and projections also differ along the rostral-caudal axis of VP (Groenewegen et al., 1993; Kupchik & Kalivas, 2013), and VP cell types are differentially implicated in drug-seeking behavior across experimental phases (Heinsbroek et al., 2020). Thus, further investigations into NAshell, IC, and VP using the finely-grained approaches discussed above would seem likely to reveal distinct subregions or populations within each nucleus that are drug selective or shared between drug and natural rewards.

Conclusions

This review summarized findings from investigations on the role of canonical addiction circuitry in regulating behavior motivated by drug versus natural reward. Brain regions were characterized as part of a drug selective circuit (i.e., the given nucleus was necessary for the initiation or execution of behavior motivated by drug but not natural reward), or the brain region was included in a shared circuit (i.e., the given region was necessary for both drug and natural reward seeking). Evidence for drug selectivity was found in NAcore, PL, IL, BNST, CeA, VTA and LH while shared circuitry included the BLA, HIPP and STN. Additionally the NAshell, IC and VP were considered mixed, presumably because these brain regions contain a connectomic or topographic mixture of both circuits that was not specifically targeted in the studies to date. Based on these findings and extant work in the addiction field, we proposed a preliminary circuit hypothesized to be necessary selectively for drug-motivated behavior. Together, drug selective neuroplasticity and functional dysregulation in the drug selective circuitry can account for many of the behavioral symptoms used to diagnose SUDs in humans. Thus, this circuitry provides a rich testing arena in which to reveal the neurobiological mechanisms of SUDs and evaluate novel therapeutic approaches for SUDs that may not influence the adaptive behaviors engendered by natural rewards. We also reviewed promising behavioral and biological techniques that will advance our understanding of how drugs of abuse, but not natural rewards, produce pathological behaviors characteristic of SUDs. More specifically, these techniques promise to reveal how even though each nucleus likely encodes both natural and drug reward in distinct subcircuits and neuronal ensembles, drug use modifies the drug selective circuits and ensembles to promote a cardinal symptom of SUDs, choosing drug reward over natural reward.

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Abbreviations:

ACC	anterior cingulate cortex
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMY	amygdala
BLA	basolateral amygdala
BNST	bed nucleus of the stria terminalis
CeA	central nucleus of the amygdala
CPP	conditioned place preference
CRF	corticotropin releasing factor
GABA	gamma-aminobutyric acid
GLT	glutamate transporter
HIPP	hippocampus
HR	high responder
IC	insular cortex
IL	infralimbic cortex
LH	lateral hypothalamus
LR	low responder
mGluR	metabotropic glutamate receptor
LTP	long-term potentiation
mPFC	medial prefrontal cortex
MSN	medium spiny neuron
NAc	nucleus accumbens
NAcore	nucleus accumbens core
NAshell	nucleus accumbens shell
NMDA	n-methyl-d-aspartate
OFC	orbitofrontal cortex

ovBNST	oval bed nucleus of the stria terminalis
PFC	prefrontal cortex
PL	prelimbic cortex
SA	self-administration
SN	subtantia nigra
STN	subthalamic nucleus
SUD	substance use disorder
VP	ventral pallidum
VTA	ventral tegmental area
xCT	cystine glutamate antiporter

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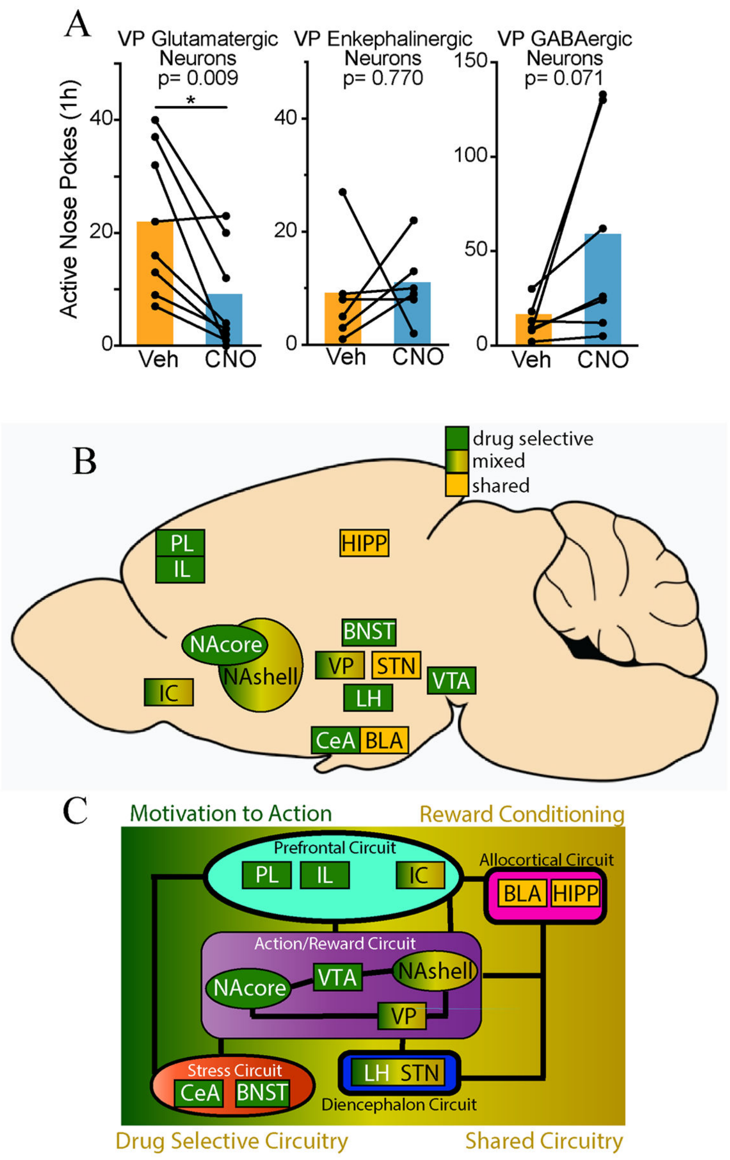
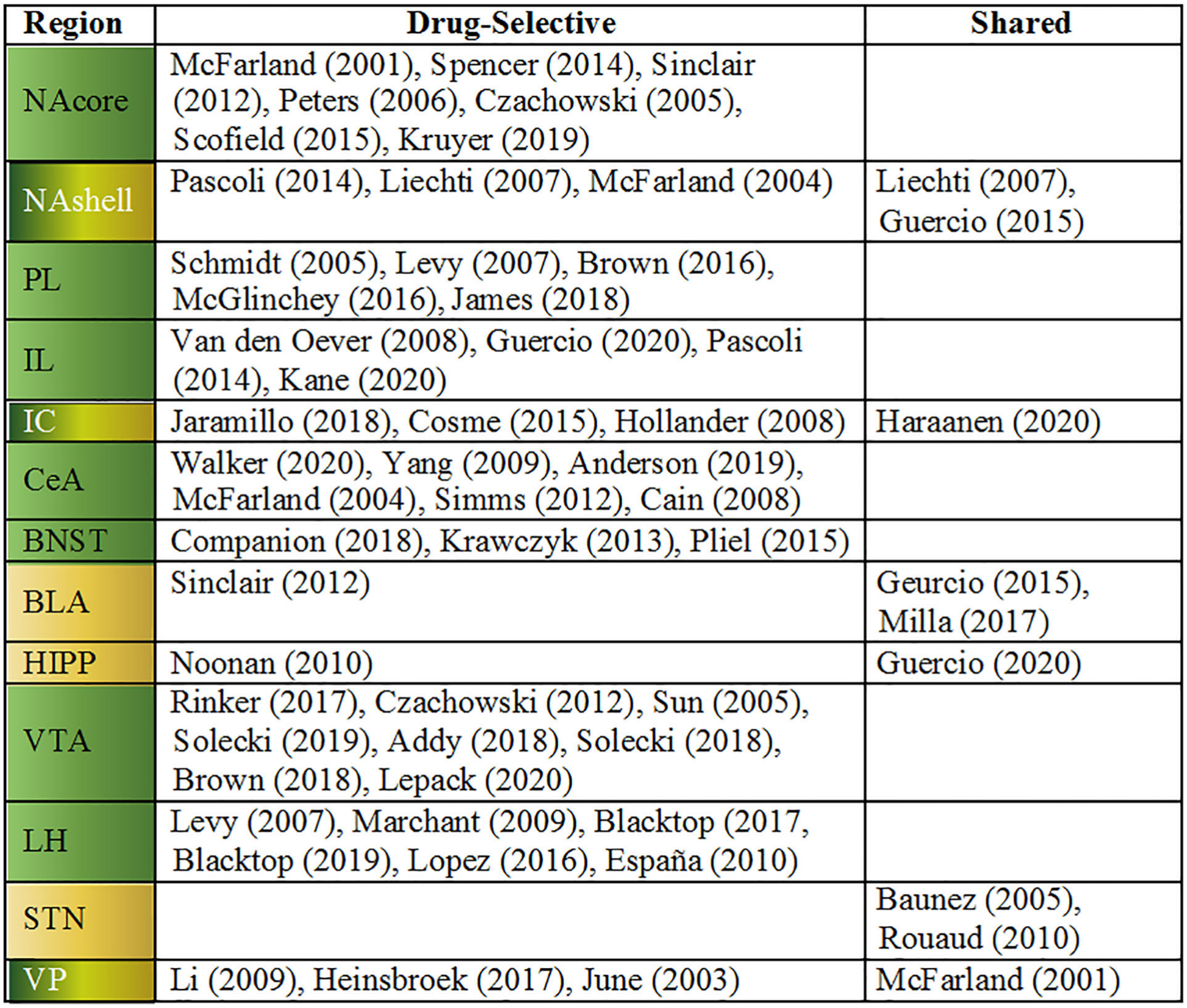

A
VP Glutamatergic Neurons
p= 0.009
*
VP Enkephalinergic Neurons
p= 0.770
VP GABAergic Neurons
p= 0.071
Active Nose Pokes (1h)
0
20
40
150
100
50
Veh
CNO
B
drug selective
mixed
shared
PL
IL
HIPP
NAcore
NAshell
IC
BNST
VP
STN
LH
VTA
CeA
BLA
C
Motivation to Action
Reward Conditioning
Prefrontal Circuit
PL
IL
IC
Allocortical Circuit
BLA
HIPP
Action/Reward Circuit
NAcore
VTA
NAshell
VP
Stress Circuit
CeA
BNST
LH
STN
Diencephalon Circuit
Drug Selective Circuitry
Shared Circuitry

Table 1:

Evidence for drug-selective and shared circuitry in NAc and NAc-connected region



Region	Drug-Selective	Shared
NAcore	McFarland (2001), Spencer (2014), Sinclair (2012), Peters (2006), Czachowski (2005), Scofield (2015), Kruyer (2019)	
NAshell	Pascoli (2014), Liechti (2007), McFarland (2004)	Liechti (2007), Guercio (2015)
PL	Schmidt (2005), Levy (2007), Brown (2016), McGlinchey (2016), James (2018)	
IL	Van den Oever (2008), Guercio (2020), Pascoli (2014), Kane (2020)	
IC	Jaramillo (2018), Cosme (2015), Hollander (2008)	Haraanen (2020)
CeA	Walker (2020), Yang (2009), Anderson (2019), McFarland (2004), Simms (2012), Cain (2008)	
BNST	Companion (2018), Krawczyk (2013), Pliel (2015)	
BLA	Sinclair (2012)	Geurcio (2015), Milla (2017)
HIPP	Noonan (2010)	Guercio (2020)
VTA	Rinker (2017), Czachowski (2012), Sun (2005), Solecki (2019), Addy (2018), Solecki (2018), Brown (2018), Lepack (2020)	
LH	Levy (2007), Marchant (2009), Blacktop (2017, Blacktop (2019), Lopez (2016), España (2010)	
STN		Baunez (2005), Rouaud (2010)
VP	Li (2009), Heinsbroek (2017), June (2003)	McFarland (2001)

Evidence for necessity of reviewed regions for drug and natural reward behaviors. Dark green = drug-selective (100% studies showed drug selectivity), Yellow/Green gradient = mixed (>50% studies showed drug selectivity), yellow = shared (≤50% studies showed drug selectivity). Abbreviations: BLA = basolateral amygdala, BNST = bed nucleus of the stria terminalis, CeA = central nucleus of the amygdala, HIPP = hippocampus, IL = infralimbic cortex, IC = insular cortex, LH = lateral hypothalamus, NAcore = nucleus accumbens core, NAshell = nucleus accumbens shell, PL = prelimbic cortex, STN = subthalamic nucleus, VP = ventral pallidum, VTA = ventral tegmental area.