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Modeling Cocaine Relapse in Rodents: Behavioral Considerations and Circuit Mechanisms

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Abstract

Addiction is a chronic relapsing disorder, in that most addicted individuals who choose to quit taking drugs fail to maintain abstinence in the long-term. Relapse is especially likely when recovering addicts encounter risk factors like small “priming” doses of drug, stress, or drug-associated cues and locations. In rodents, these same factors reinstate cocaine seeking after a period of abstinence, and extensive preclinical work has used priming, stress, or cue reinstatement models to uncover brain circuits underlying cocaine reinstatement. Here, we review common rat models of cocaine relapse, and discuss how specific features of each model influence the neural circuits recruited during reinstated drug seeking. To illustrate this point, we highlight the surprisingly specific roles played by ventral pallidum subcircuits in cocaine seeking reinstated by either cocaine-associated cues, or cocaine itself. One goal of such studies is to identify, and eventually to reverse the specific circuit activity that underlies the inability of some humans to control their drug use. Based on preclinical findings, we posit that circuit activity in humans also differs based on the triggers that precipitate craving and relapse, and that associated neural responses could help predict the triggers most likely to elicit relapse in a given person. If so, examining circuit activity could facilitate diagnosis of subgroups of addicted people, allowing individualized treatment based on the most problematic risk factors.

Keywords

neural circuits; reinstatement; self-administration; ventral pallidum; voluntary abstinence

1. Introduction

Drug addiction is characterized by a transition from controlled drug use to compulsive intake, often accompanied by extreme difficulty in quitting, and especially in maintaining abstinence. Most quit attempts result in relapse to active use within a year, and recovering addicts typically make multiple transitions between drug abuse and abstinence in the first year after deciding to quit (McLellan et al., 2000). This propensity for relapse persists long

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after the affective or physical symptoms of withdrawal subside, yet no effective treatments exist for reducing risk of relapse to psychostimulants, and few exist for any drug of abuse (Czoty et al., 2016; Shorter et al., 2015). Clearly, a great need exists for next-generation, neuroscience-based clinical approaches for intervening in this devastating disorder, but this will first require a better understanding of the brain substrates of relapse. Unfortunately, human research is limited by a lack of means to manipulate or observe neural activity at the cellular and circuit levels *in vivo*, where addiction-related changes are most likely to manifest, and therefore where future brain-based interventions are most likely to succeed.

Fortunately, behavioral features of addiction including drug intake and relapse are amenable to modeling in animals. Rats and mice readily self-administer the same psychoactive drugs as humans including cocaine, and following a period of abstinence, reinstate their drug seeking when exposed to the same factors that put humans at risk of relapse—drug-associated cues, “priming” doses of the drug, and stress. Crucially, the specific features of rodent relapse models influence which neural circuits are recruited, and this fact may also have implications for predicting which circuits are involved when humans fail to resist temptation to take drugs.

Here we provide an overview of commonly used rodent drug self-administration and reinstatement models, and describe how the neural circuits underlying renewed cocaine seeking vary based on experimental details like the type of relapse trigger that initiates cocaine seeking. Self-administration procedures and means of achieving abstinence from drug also affect circuits involved in subsequently tested reinstatement, but the details of this are poorly understood to date, so we focus here on circuit heterogeneities stemming from different relapse modalities. It is our hope that by mapping circuits engaged during a variety of relapse-related behaviors in rodents, we can make better predictions of those most likely to be involved in individuals when they encounter particular stimuli that put them at risk of returning to problematic drug use.

2. Cocaine self-administration models

Drug self-administration has become a gold standard in preclinical addiction research, owing to the overt similarity of this behavior to human voluntary drug intake (Shaham et al., 2003). Rodents are trained to perform an operant response (e.g., lever press or nose poke) for a dose of drug, typically accompanied by a concurrently-delivered, discrete cue such as a light and a tone. Like humans, individual rats vary in their propensity to acquire self-administration and in their preferred level of intoxication, and such individual variation relates to other addiction-relevant behaviors including subsequent reinstatement (Belin et al., 2009; Piazza et al., 2000; Bentzley et al., 2014).

The effort required to obtain cocaine influences the neural circuits engaged, for example those underlying high-effort, highly motivated seeking are dissociable from those underlying low effort self-administration (Floresco et al., 2008; Kurniawan et al., 2011). Most rodent relapse studies employ low effort self-administration schedules like fixed ratio 1, where one lever press yields one intravenous cocaine infusion. Under this schedule, rats typically “load up” on cocaine at the beginning of each session until preferred cocaine blood levels are

reached (this level is sometimes referred to as the rats' "hedonic set point"), then doses are self-administered regularly throughout the rest of the session in order to maintain this level of intoxication (Olmstead et al., 2000; Roberts et al., 2013; Suto and Wise, 2011). This phenomenon may also occur in humans during cocaine binging (Sughondhabirom et al., 2005), though not necessarily under all laboratory conditions (Angarita et al., 2010).

To study highly motivated, addiction-like pursuit of cocaine, more complex procedures employing higher response requirements have been developed. For example, in the progressive ratio task, effort required for reward increases incrementally throughout the session until the animal gives up on seeking (Hodos, 1961). The maximum response schedule an animal performs within a set timeframe for a fixed dose of cocaine is called its "breakpoint," which reflects its level of motivation for cocaine.

Another factor that affects cocaine self-administration behavior is the duration, quantity, and pattern of drug use experience. Preferred daily cocaine blood levels increase with extended use, presumably due to tolerance, and motivation to pursue cocaine also increases in some rats with repeated long-access intake. For example, weeks of long access (~6 hrs/day), relative to short access (~2 hrs/day) to cocaine escalates daily intake in most animals (Ahmed and Koob, 1998), increases motivation to maintain cocaine intoxication, and decreases sensitivity of intake to punishment, e.g. shock delivered concurrently with cocaine (Ahmed et al., 2013; Edwards and Koob, 2013; Kawa et al., 2016; Koob and Kreek, 2007; Mantsch et al., 2016; Vanderschuren and Everitt, 2004). Such intake escalation is associated with alterations in the neural circuits underlying self-administration. For instance, escalation of cocaine intake under long access conditions may result from attenuated ventral striatal phasic dopamine responses when animals perform an operant response for cocaine, since observed DA responses decrease most in escalating animals, and boosting DA responses with l-dopa attenuates escalated seeking (Willuhn et al., 2014). However, we note that long access to cocaine is not necessary for development of compulsive drug seeking in rats, since susceptible individuals show compulsive seeking even after short-access continuous self-administration (Pelloux et al., 2012). In addition, intermittent access (and concomitant rapid spiking of cocaine blood levels) is as effective as extended access for promoting compulsive drug seeking, even when far less drug is taken. For example, cocaine economic demand, breakpoint, and cue-triggered reinstatement are increased to a similar extent in long- and intermittent-access animals (Allain et al., 2017a; Kawa et al., 2016; Zimmer et al., 2012). This shows that the pattern of drug intake is at least as important as total amount of drug taken for inducing an addiction-like phenotype (Allain et al., 2017b; Samaha and Robinson, 2005).

3. Modeling cessation of cocaine use

By definition, relapse follows cessation of drug use, and the means by which abstinence is achieved may affect the circuitry underlying subsequent reinstatement (Bossert et al., 2013; Fuchs et al., 2006; Venniro et al., 2017). In humans, cocaine abstinence occurs either voluntarily (e.g., choosing to cease problematic use) or involuntarily (e.g., imprisonment, non-voluntary rehabilitation treatment), and both situations have been modeled in rodent studies. The most commonly used preclinical relapse models employ either forced

abstinence or extinction training to model cessation of drug use, though self-imposed abstinence models are also gaining popularity due to their face validity for modeling humans who decide to try to quit using drugs.

3.1. Forced abstinence

Forced abstinence entails removing rodents from the drug exposure context entirely by imposing a period of abstinence. Following this homecage abstinence period, animals are re-introduced to the drug context, and tested for drug seeking under extinction conditions. Relative to 1 day of abstinence, 1-4 weeks abstinence increases responding during this initial extinction test, with or without a cocaine priming injection (Neisewander et al., 2000; Tran-Nguyen et al., 1998). Grimm and colleagues (2001) went on to find that the length of this abstinence period also increases cue-induced cocaine seeking, a phenomenon they termed “incubation of craving.” This heightened cue-induced drug seeking occurred after long periods (days to months) of abstinence, relative to shorter abstinence periods (e.g., 1 day), though this effect degrades with very long abstinence periods (e.g., 180 days) (Lu et al., 2004), possibly due to memory degradation. A similar craving incubation effect is also observed in humans with several drugs of abuse (Bedi et al., 2011; Gawin and Kleber, 1986; Li et al., 2015; Parvaz et al., 2016; Wang et al., 2013). Incubation of craving may result from drug-associated memories becoming increasingly salient, and therefore liable to initiate robust drug seeking; a phenomenon that could help explain why relapse risk remains high long after quitting drugs.

3.2. Extinction-based abstinence

A common means of inducing abstinence in rodent relapse experiments is via extinction training. In extinction, operant responding no longer elicits drug delivery or cues, so animals learn to stop responding for drug (de Wit and Stewart, 1981). Extinction memories (both appetitive and aversive) do not overwrite the initial memories they suppress, but are instead mediated by anatomically distinct circuits that suppress the circuits underlying drug seeking (Bouton et al., 2006; LaLumiere et al., 2010; Peters et al., 2009; Quirk et al., 2006). Notably, drug seeking during extinction is reduced mainly by lack of drug availability despite ongoing motivation to use (and lack of reasons not to use), which may be most relevant to humans that would like to continue using drugs, but cannot. Some have speculated that strengthening these extinction memories, and/or manipulating reconsolidation of extinction or drug memories in psychotherapy may be effective at helping people maintain abstinence (Everitt, 2014; Kalivas and Volkow, 2011; McNally, 2014; Millan et al., 2011; Nic Dhonnchadha and Kantak, 2011; Xue et al., 2012), though evidence supporting efficacy of this strategy is mixed to date (Conklin and Tiffany, 2002; Kaplan et al., 2011; Konova et al., 2017; Kredlow et al., 2016).

3.3. Self-imposed abstinence

Forced- and extinction-based abstinence protocols, while experimentally convenient and commonly used in rodent studies, fail to capture the voluntary nature of abstinence that is characteristic of most humans who choose to quit using drugs. For this reason, the Yavin Shaham group and others have developed procedures allowing rodents to choose to quit taking drugs prior to reinstatement testing. For example, rats will cease self-administering

cocaine when mutually-exclusive alternative rewards such as food are offered, or when drug is delivered in conjunction with a punishing stimulus such as a shock (Ahmed, 2010, 2012; Caprioli et al., 2015; Lenoir et al., 2013; Marchant et al., 2013a, 2013b; Pelloux et al., 2017; Venniro et al., 2016). We will discuss these models further in Section 7 below.

4. Reinstatement models

In humans, craving and subsequent relapse is often precipitated by ingestion of a small priming dose of drug, experiencing acute stress, or encountering discrete or contextual cues previously paired with drug use (O'Brien et al., 1998; Shaham et al., 2003; Sinha et al., 2011). Humans and rodents both vary individually in their sensitivity to these triggers (Bentzley et al., 2014; Homberg et al., 2004; McKay et al., 1996), and mounting evidence points to distinct neural circuits underlying relapse initiated by each. Therefore, we next describe common rodent models of cocaine reinstatement, most commonly tested following extinction training.

4.1. Cocaine-primed reinstatement

A small priming dose of drug in an abstinent individual can elicit craving, and increases risk of full-blown relapse (Donny et al., 2004; Stewart, 2000). Priming doses of cocaine also reinstate drug seeking in abstinent rats (de Wit and Stewart, 1981; Shaham et al., 2003). Importantly, cocaine selectively promotes cocaine seeking in rats, but not seeking of an alternative reward (food), demonstrating specificity of priming for enhancing motivation for cocaine in particular (Tunstall and Kearns, 2014). However, we note that cocaine dose must be carefully chosen for priming experiments in rodents, since higher doses (>15mg/kg) can induce behavioral stereotypies or other nonspecific locomotion that competes with drug seeking.

4.2. Stress reinstatement

Another significant relapse risk factor in humans is exposure to stress (Sinha et al., 2011). In rodents, acute stressors such as footshock, forced swimming, food deprivation, and administration of the aversive alpha-2 norepinephrine (NE) antagonist yohimbine (considered a 'pharmacological stressor') precipitate reinstatement (for reviews, see Mantsch et al., 2016; See and Waters, 2011; Shaham et al., 2000; Shalev et al., 2010). Acute delivery of intermittent footshock is perhaps the most widely used stress reinstatement model. Typically, animals are trained to self-administer drug with discrete response-contingent cues, extinguished of this behavior, then unpredictable footshocks are administered immediately prior to a cue reinstatement test. The efficacy of intermittent shock as a reinstatement trigger depends upon multiple factors including pre-shock stress levels, the amount of drug access during self-administration training, and whether the animal lives in the operant chamber or in a separate cage (Mantsch et al., 2016; Shalev et al., 2010). These sensitivities likely reflect the highly context-dependent nature of rodent stress responses, only some of which result in renewed drug seeking. The extent to which this is also true in humans is not clear, but we expect that likewise, certain types of stress are especially effective in inducing cocaine seeking in recovering addicts. To study this

possibility in rats, a new test of psychosocial stress-induced relapse was developed, in which stimuli paired with social defeat robustly reinstate cocaine seeking (Manvich et al., 2016).

4.3. Cue- and context-induced reinstatement

Environments and sensory cues associated with drug-taking acquire *incentive salience*, or an attractive, desirable quality similar to the unconditioned rewards they predict (Berridge, 2001; Bindra, 1978). A drug-associated cue that has acquired incentive salience becomes a potent motivational trigger, and even after long-term abstinence it can capture the attention of a recovering addict, eliciting craving and temptation to relapse (Courtney et al., 2016; O'Brien et al., 1998). Cues can be either diffuse and multimodal (“context cues”) or physically localized and temporally coincident with drug (“discrete cues”), and thinking about or viewing either type of cue elicits craving in humans (Bonson et al., 2002; Courtney et al., 2016; O'Brien et al., 1998; Sinha et al., 2011; Sinha and Li, 2007).

However, context and discrete cues have importantly different features. For example, a context cue in humans might be visiting a house or neighborhood where one used to take drugs. In rodents, context reinstatement usually takes the form of “ABA” testing in which a rat is trained to self-administer cocaine in Context A, extinguished in a distinct Context B, then returned to Context A, where lever pressing is measured in the absence of drug (Bouton and Bolles, 1979; Crombag et al., 2002).

In contrast, discrete cocaine cues in humans include the feeling of cocaine-induced nasal numbing, or the sight and smell of cocaine—both stimuli experienced in close temporal association with the onset of drug effects. Such cocaine-coincident discrete cues have conditioned reinforcing properties in humans; for example smokers will smoke denicotinized cigarettes (Rose, 2006). Cocaine users also report drug-like subjective effects after experiencing stimuli associated with drug taking (Ehrman et al., 1992; O'Brien et al., 1998), which likely contributes to their conditioned reinforcing properties. To model discrete cue-induced conditioned reinforcement in rats, they can be trained to pair intravenous cocaine with a coincident temporally-discrete cue. In most studies, instrumental responses during training are rewarded with cocaine and a cue during self-administration training, but cue/cocaine pairings can alternatively be made apart from instrumental training in a separate Pavlovian training session, allowing experimental dissociation of Pavlovian and instrumental learning mechanisms (Kruzich et al., 2001; Smith et al., 2009a). Most rats show cocaine seeking when such discrete cocaine cues are delivered response-contingently during a drug-free reinstatement test, and this conditioned reinforcement-based model is commonly used since it elicits robust drug seeking behavior (Kruzich et al., 2001).

5. Cocaine reinstatement circuits—Devil in the details

Craving and relapse in humans, like renewed drug seeking after abstinence in rodents, is often assumed to be unitary in nature, and to involve specific neural circuits regardless of how reinstatement is elicited. An implication of this assumption is that if aberrant, addiction-related circuit activity could be reversed, relapse could be prevented. However, animal studies show that the brain circuits which are activated by and necessary for reinstatement under different circumstances are not completely overlapping. If this is also true in humans,

it could have important implications for treating patients that vary in their susceptibility to the relapse-promoting properties of drug priming, stress, or cues (Carter and Tiffany, 1999; Flagel et al., 2009; Mahler and de Wit, 2010; Sinha et al., 2011). As mentioned above, the means by which abstinence is induced prior to reinstatement in rodent studies can also influence the neural pathways involved (Fuchs et al., 2006; Bossert et al., 2013; Venniro et al., 2017; Ma et al., 2014). Therefore, we contend that a fuller understanding of circuit/behavior relationships in rodent relapse models may inform hypotheses about the specific neural circuits that are engaged when humans encounter relapse risk factors.

Next, we briefly review the neural circuits underlying reinstatement of cocaine seeking in self-administration-based cocaine relapse models in rats. Several excellent reviews cover these relapse circuits in more detail (Bossert et al., 2013; Kalivas and McFarland, 2003; Lasseter et al., 2010a; Shalev et al., 2002; Weiss, 2005), and here we emphasize rodent findings showing that circuit involvement varies based upon experimental conditions, highlighting the fact that not all cocaine relapse is alike in the brain.

5.1. Circuitry common across post-extinction reinstatement modalities

Despite circuit heterogeneities described below, at least one neural circuit; a pathway involving ventral tegmental area (VTA) DA projections to prelimbic medial prefrontal cortex (PLC), PLC projections to nucleus accumbens core (NAcCo), and NAcCo projections to VP circuit has been described as a “final common pathway” of reinstatement (Kalivas and Volkow, 2005). This circuit is required for cocaine, stress, and cues to elicit cocaine seeking, at least following extinction training (Fig. 1). For example, temporary pharmacological inactivation of PLC or NAcCo, or excitotoxic lesions of either region block prime-, stress-, and discrete cue-induced reinstatement of cocaine seeking (Kalivas, 2008; Shaham et al., 2003), as does optogenetic inhibition or pharmacological disconnection of PLC-NAcCo projections (McGlinchey et al., 2016; Stefanik et al., 2013a). PLC-NAc projections (as well as BLA-NAc projections) also undergo plasticity during forced abstinence that results in “silent synapses,” or newly formed synaptic connections. When mature, these synapses facilitate robust cocaine seeking, unlike ILC-NAc projections, where abstinence-induced silent synapses instead suppress cocaine seeking (Ma et al., 2014; Lee et al., 2013). NAc’s major output, VP, is also required for primed, stress, and discrete cue reinstatement, which will be discussed in more detail below. VTA DA neuron projections to forebrain nuclei including PLC, orbitofrontal cortex (OFC), NAc, and basolateral amygdala (BLA) also modulate many types of cocaine reinstatement following extinction training, though DA in some of these pathways is necessary for only certain relapse modalities (Bachtell et al., 2005; Bossert et al., 2013; Capriles et al., 2003; McFarland et al., 2004; McFarland and Kalivas, 2001; See et al., 2001; Shaham et al., 2003). DA in PLC, though, is involved in all types of post-extinction cocaine reinstatement, including primed (McFarland and Kalivas, 2001), stress-induced (Capriles et al., 2003), and cue-induced (McGlinchey et al., 2016).

5.2. Cocaine primed reinstatement circuits

Cocaine’s main mechanism of action is to block monoaminergic transporters, and cocaine-primed reinstatement is unsurprisingly dependent upon intact monoamine neurotransmission. DA transporters in particular are crucial for cocaine’s ability to induce

cocaine-primed reinstatement (Schmidt et al., 2005) by increasing synaptic DA levels by slowing its clearance from the synaptic cleft. Both self-administered and non-contingent cocaine increase the frequency of DA transients and extracellular levels in rat NAc *in vivo* (Stuber et al., 2005; Willuhn et al., 2012), and, consistent with this, pharmacological suppression of all VTA neuronal activity blocks cocaine-primed reinstatement (McFarland and Kalivas, 2001).

Cocaine-induced DA and other monoamines are implicated in the priming effects of cocaine in a complex manner (Fig. 1A) (Schmidt et al., 2005). Systemically, DA receptor 2 (D2; inhibitory, G_{i/o}-coupled) activity generally promotes reinstatement—a D2 agonist induces, and a D2 antagonist attenuates primed reinstatement (Schenk and Gittings, 2003; Self et al., 1996; Spealman et al., 1999). Paradoxically, both agonists and antagonists of DA receptor 1 (D1; stimulatory, G_s-coupled) reduce cocaine-primed reinstatement (Alleweireldt et al., 2003; Self et al., 1996; Spealman et al., 1999). These findings may be explained by distinct roles for DA receptors in individual forebrain regions in cocaine priming effects. In NAcCo, a mixed D1/2 antagonist blocks cocaine primed reinstatement (McFarland and Kalivas, 2001), and blockade of both D1 and D2 in NAc shell (NAcSh) also do so (Anderson et al., 2003, 2006), and agonists of both receptors conversely induce reinstatement (Schmidt et al., 2006). D2 but not D1 stimulation in central amygdala nucleus (CeA) reduces cocaine priming (Thiel et al., 2010), as does blockade of PLC D1 and D2 receptors (McFarland and Kalivas, 2001; Sun and Rebec, 2005, but see Capriles et al., 2003), or inhibiting PLC alpha-1 NE receptors (Schmidt et al., 2017).

In addition, 5-hydroxytryptamine (5HT/serotonin) receptors modulate cocaine-primed reinstatement, since systemic 5HT_{2A} antagonism in monkeys, and 5HT_{1A} blockade or 5HT_{2C} stimulation in rat CeA suppress cocaine primed seeking (Burmeister et al., 2004; Murnane et al., 2013; Pockros-Burgess et al., 2014). Kappa opioid stimulation in VTA also suppresses cocaine-primed reinstatement (Sun et al., 2010), likely via inhibition of DA neurons there (Margolis et al., 2003). Of note, cocaine priming effects also rely in part on conditioned reactions to cocaine's subjective and physiological effects, including its peripheral autonomic actions (Wise and Kiyatkin, 2011). In sum, cocaine priming effects rely upon monoaminergic and other systems involved in mediating cocaine's acute effects, and we note that the circuits of cocaine priming are likely to differ from priming effects of other drugs of abuse with actions via other neural mechanisms.

5.3. Stress-specific circuits

The brain's major stress systems like NE, corticotropin-releasing factor (CRF), and kappa opioid receptors are heavily involved in stress-induced reinstatement of cocaine seeking, especially in extended amygdala, VTA, and lateral hypothalamus (LH) (Fig. 1B) (for comprehensive reviews, see Mantsch et al., 2016; McReynolds et al., 2014; Shalev et al., 2010; Sinha et al., 2011; Smith and Aston-Jones, 2008). Involvement of these circuits differentiate stress from other types of reinstatement, although we also point out a significant overlap in stress- and cue-related reinstatement circuits.

NE neurotransmission in stress- and aversion-related emotional circuits, including CeA and bed nucleus of the stria terminalis (BNST), are crucial for stress reinstatement of cocaine

seeking. Systemic alpha-2 receptor stimulation (decreasing NE release), or intra-CeA or BNST β 1/2 antagonism (blocking NE postsynaptic signaling) attenuates stress-, but not cocaine-primed reinstatement, while BNST β 2 stimulation conversely induces reinstatement (Erb et al., 2000; Leri et al., 2002; Vranjkovic et al., 2014). Decreasing NE synthesis also decreases stress reinstatement (footshock and yohimbine), but also other types of reinstatement (Schroeder et al., 2013). In general, these findings are consistent with extended amygdala NE's general role in aversive and arousal-related aspects of stress, as well as stress that induces cocaine seeking (España et al., 2016; Smith and Aston-Jones, 2011).

CRF systems (sometimes recruited by NE; Brown et al., 2009; Mantsch et al., 2016) are heavily implicated in stress-induced cocaine reinstatement, especially via CeA-BNST projections. Systemic or intracerebroventricular (i.c.v.) administration of CRF receptor antagonists attenuates footshock reinstatement, while i.c.v. CRF induces it (Erb et al., 1998; 2006). CRF in BNST is necessary and sufficient for footshock reinstatement (Erb and Stewart, 1999), and this CRF comes at least in part from CeA, since unilateral CeA inactivation, and contralateral BNST CRF antagonist blocks cocaine seeking (Erb et al., 2001a). In contrast, neither CRF signaling nor neural activity in BLA is required for footshock reinstatement, indicating specificity for stress reinstatement to extended amygdala, rather than cortical amygdala (Erb and Stewart, 1999; McFarland et al., 2004).

VTA is another site where CRF plays a role in stress reinstatement of cocaine seeking. Knockdown of VTA CRF1 receptors blocks footshock reinstatement (Chen et al., 2014), and intra-VTA CRF reinstates cocaine seeking by facilitating glutamate and dopamine release there (Wang et al., 2005). In cocaine-experienced rats, CRF together with γ -Aminobutyric acid (GABA) B receptor signaling presynaptically modulate VTA GABA and glutamate release, facilitating DA neuron excitation and cocaine relapse (Blacktop et al., 2016; Williams et al., 2014; Wise and Morales, 2010). VTA CRF may result from β 2 NE receptor stimulation in BNST, as antagonism of β 2 NE receptors in unilateral BNST, and concurrent CRF blockade in contralateral VTA attenuates footshock reinstatement (Vranjkovic et al., 2014). In sum, CRF plays a major role in inducing reinstatement of cocaine seeking after stress in both extended amygdala and VTA, and likely in other untested regions as well.

Kappa opioid receptors, and their endogenous ligand dynorphin, are also involved in stress-induced reinstatement of cocaine seeking, in part via actions in VTA and BNST. Systemic kappa opioid receptor antagonists abolish footshock or forced swim stress-induced, but not cocaine-primed reinstatement (Beardsley et al., 2005; Polter et al., 2014). This may result from kappa modulation of GABAergic inputs to VTA DA neurons (Graziane et al., 2013), or direct inhibition of DA neurons themselves (Margolis et al., 2003).

LH orexin neurons are involved in arousal, stress, and motivation-related processes (Alexandre et al., 2013; Berridge et al., 2010; Calipari and España, 2012; Mahler et al., 2014a), and also play a role in stress-induced cocaine reinstatement, in part via their VTA and CeA projections. Orexin projections to VTA are necessary for stress reinstatement (Boutrel et al., 2005; Tung et al., 2016), while intra-VTA orexin_A conversely induces reinstatement (Wang et al., 2009). This likely involves direct orexin excitation of VTA DA

neurons (España et al., 2010; Korotkova et al., 2003), as well as interactions with VTA glutamate, GABA, and endocannabinoids (Borgland et al., 2006; Mahler et al., 2013; Tung et al., 2016). Orexin in CeA is also required for yohimbine-induced reinstatement (Schmeichel et al., 2017), potentially by recruiting CRF neurons there (Erb et al., 2001b). Intriguingly, dynorphin (the main endogenous kappa opioid receptor ligand) is co-synthesized by all LH orexin neurons (Chou et al., 2001) and both dynorphin and orexin are co-released in VTA and paraventricular thalamus (PVT), where they play roles in aversion, reward, and cocaine reinstatement (Baimel and Borgland, 2017; Matzeu et al., 2017; Muschamp et al., 2014). Further research should explore how kappa and orexin signaling in VTA, PVT, and elsewhere interact to modulate stress-induced reinstatement after cocaine self-administration.

5.4. Context cue-specific circuits

In humans, revisiting places where drugs were previously used often causes craving, and potentially, relapse. In rodents, exposure to cocaine-paired places also elicits robust reinstatement (for in-depth reviews, see (Bossert et al., 2013; Crombag et al., 2008; Khoo et al., 2017; Lasseter et al., 2010a; Marchant et al., 2015). Although there is much overlap in discrete learned cue- and context-reinstatement circuitry, some differences exist between the two, particularly in the roles played by hippocampus and connected cortical regions (Fig. 1C, D).

Dorsal and ventral hippocampal circuits both play important roles in context-induced reinstatement of cocaine seeking. Inactivation of ventral hippocampus proper, but not of the hippocampal dentate gyrus, blocks the ability of contextual or response-contingent discrete cues, or cocaine prime, to cause reinstatement (Lasseter et al., 2010b; Rogers and See, 2007), suggesting a general role for ventral hippocampus in conditioned emotion/motivation. This is consistent with other evidence that ventral hippocampus mediates emotional or motivational components of spatial memory (Fanselow and Dong, 2010). In contrast, inactivation, or metabotropic glutamate receptor 1 (mGluR₁) blockade in dorsal hippocampus attenuates only context reinstatement, without affecting reinstatement elicited by discrete cues or cocaine (Fuchs et al., 2005; Xie et al., 2010), in line with its general role in spatial memory (Fanselow and Dong, 2010; Moser and Moser, 1998). In other words, dorsal hippocampus (analogous to caudal hippocampus in human) is likely required for rodents to know where they are, and to use that information to trigger drug seeking, while ventral hippocampus may play a larger role in affective memory and motivation during reinstatement.

Hippocampus anchors a wider corticolimbic network that supports cocaine context-induced reinstatement (Fig. 1C). BLA, dorsomedial PFC, and lateral OFC are required, as is communication between dorsal hippocampus and these structures, and DA input (via D1 receptors) to OFC (Fuchs et al., 2005, 2007; Lasseter et al., 2010a, 2011a, 2014; Wells et al., 2011). Additionally, dorsal (but not ventral) hippocampus promotes cocaine reinstatement by indirectly disinhibiting VTA DA neurons, via innervation of lateral septum GABA neurons that project to VTA GABA interneurons (Luo et al., 2011), a pathway that is not required for discrete cue reinstatement (McGlinchey and Aston-Jones, 2017). Glutamate

signaling in both NAcCo and NAcSh are also required for context reinstatement (Xie et al., 2012). In addition, systemic orexin receptor 1 (OX1R) antagonism blocks cocaine context reinstatement (Smith et al., 2010), and exposure to a cocaine-paired context (relative to an extinguished context) induces Fos expression in LH, but surprisingly, not in either orexin or melanin-concentrating hormone neurons there (Hamlin et al., 2007). In sum, the circuits that specifically subserve context reinstatement involve both spatial memory networks for identifying specific locations and environments, as well as conditioned motivation circuits.

5.5. Discrete cue-specific circuits

Cues temporally paired with cocaine elicit reinstatement via a network of cortical and subcortical regions, some of which are specific to conditioned cocaine seeking, and some of which overlap with other reinstatement circuits (Fig. 1D). BLA plays a general role in Pavlovian learning and motivation, and Fos expression there is correlated with the magnitude of cued reinstatement in male and female rats (Kufahl et al., 2009; Zhou et al., 2014). Accordingly, BLA lesion or inactivation blocks reinstatement elicited by either discrete or contextual cues (See et al., 2003). BLA's role in discrete cue-induced cocaine seeking is dependent upon its inputs from lateral OFC, and its projections to NAc and PLC, since optogenetic inhibition of these pathways reduces cocaine seeking (Arguello et al., 2017; Stefanik and Kalivas, 2013). DA receptors play a particularly important role in BLA modulation of cue-induced cocaine seeking, since cues elicit DA release in amygdala (Weiss et al., 2000), and BLA D1 (but not D2/3) or ionotropic glutamate receptor blockade attenuates this behavior (See et al., 2001). In contrast, BLA and mPFC projections to VTA are not Fos activated during cue-induced cocaine seeking, unlike numerous other subcortical projections to VTA, including NAcCo, subregions of NAcSh, lateral septum, VP, and extended amygdala regions including BNST (Mahler and Aston-Jones, 2012). In addition to cue-induced cocaine seeking, BLA also plays a crucial role in re-consolidating Pavlovian cocaine memories, causing some to speculate that blocking drug memory re-consolidation could be helpful for treating excessively strong memories in cocaine addiction (Everitt, 2014; Lee et al., 2005; Miller and Marshall, 2005; Rich and Torregrossa, 2017). The insular cortex, which is highly interconnected with BLA and other cue-reinstatement regions, may also play a special role in cue-induced reinstatement since inhibition of its anterior aspect blocks cued but not cocaine primed reinstatement (Cosme et al., 2015), and projections from this region to CeA are required for cued methamphetamine reinstatement.

LH orexin neurons are also implicated in discrete cue-induced reinstatement, similar to context reinstatement. For example, LH's large, mostly non-orexinergic projection to VTA is Fos activated during discrete cue reinstatement (Mahler and Aston-Jones, 2012). However, while systemic OX1R antagonism or intra-VTA OX1R blockade reduces discrete cue-induced reinstatement (James et al., 2011; Mahler et al., 2013; Smith et al., 2009a), only non-orexin LH neurons projecting to VTA are significantly Fos-activated (Mahler and Aston-Jones, 2012). It is not clear why orexin receptor signaling is required while orexin neurons are not Fos activated during cue-induced cocaine seeking, as they are during expression of conditioned place preference for cocaine or other rewards (Harris et al., 2005). This apparent disconnect could reflect intermittent orexin neuron firing during these time-locked, intermittent cue presentations that does not result in significant Fos expression

(Mahler et al., 2014a). Alternatively, it could reflect orexin's more general role in motivational activation (Mahler et al., 2014a), which is required for cue reinstatement, but also other behaviors unrelated to cocaine seeking that also occur in control groups tested in Fos expression experiments.

Regardless, in VTA orexin facilitates glutamate transmission to promote cued reinstatement of cocaine seeking. Both OX1R and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) neurotransmission are simultaneously required for discrete cues to reinstate seeking, as unilateral blockade of each receptor system in contralateral hemispheres blocks behavior, and intra-VTA OX1R antagonist-induced suppression of cue reinstatement is reversed by co-microinjection of an AMPA positive allosteric modulator (Mahler et al., 2013). These findings suggest that orexin's facilitation of ionotropic glutamate neurotransmission upon VTA DA neurons underlies its role in cued reinstatement (Borgland et al., 2006; James et al., 2017; Mahler et al., 2012). Cocaine-primed reinstatement, in contrast, is unaffected by systemic or intra-VTA blockade of OX1Rs, or VTA AMPA/N-methyl-D-aspartate (NMDA) receptors, indicating specificity of this mechanism to conditioned (and stress-induced) cocaine seeking (Boutrel et al., 2005; Mahler et al., 2013), at least in male rats (Smith et al., 2009a; Zhou et al., 2012).

It is also noteworthy that stress facilitates the ability of cues to promote cocaine seeking. Consistent with this idea, exposing human subjects to drug cues in the absence of drug availability elicits drug craving, but also strong negative affect and cortisol response (Childress et al., 1999; Mahler and de Wit, 2005; Sinha et al., 2000; Tiffany, 1990), and yohimbine increases cue-induced cocaine craving (Moran-Santa Maria et al., 2014). Importantly, stress can also increase conditioned craving responses to cues in humans in a real-world setting, particularly for cocaine (Preston et al., 2017). In rats, cues activate the hypothalamic-pituitary-adrenal axis and induce anxiety-like behavior (DeVries et al., 1998; DeVries and Pert, 1998), and reinstatement of cocaine seeking elicited by footshock or yohimbine is observed primarily when response-contingent cues are also present (Chen et al., 2015; Feltenstein and See, 2006). Furthermore, stress-related systems like NE and CRF are required for rodent cued reinstatement, as reducing NE release with alpha-2 receptor stimulation, and antagonism or knockdown of CRF1 receptors, blocks psychostimulant seeking elicited by cues (Chen et al., 2014; Moffett and Goeders, 2007; Smith and Aston-Jones, 2011). CRF in insular cortex, a region associated with addiction-related craving in humans (Naqvi et al., 2007), is also required for cue-induced seeking (Cosme et al., 2015). Anterior insula projections to CeA are also required for cue-induced reinstatement of methamphetamine seeking (Venniro et al., 2017), though the relevance of this pathway for cocaine is yet untested. In sum, the ability of stress to facilitate conditioned and habitual response strategies may be a major means by which stress alters normal and disordered behavior (Goodman and Packard, 2016; Li and Sinha, 2008; Schwabe and Wolf, 2011; Smith and Laiks, 2017). This said, not all stress is alike, nor do all individuals respond to the same stress in the same way; for example stress-sensitive rats show suppression of cue-induced cocaine seeking after re-exposure to a stress-paired environment (Hadad et al., 2016).

6. Ventral pallidum: hidden complexities in reinstatement functions

As described above, overlapping but dissociable neural circuits underlie cocaine reinstatement elicited by different relapse triggers. We next illustrate this point by focusing on the surprisingly complex roles of a single brain region, VP, in cocaine reinstatement. We highlight this region due to our recent work showing its complex mediation of cocaine reinstatement, but point out that it is but one important node in wider reinstatement circuits. Yet we predict that like in VP, similar functional-anatomical heterogeneities may also exist in other relapse-related brain regions.

VP is the Substance P-rich region caudal of NAc, ventral of the anterior commissure and globus pallidus, and rostral of extended amygdala structures like BNST and sublentiform extended amygdala in rodents (De Olmos and Heimer, 1999; Haber and Nauta, 1983; Zahm and Heimer, 1990). VP is intimately integrated within mesocorticolimbic circuits, where it is ideally positioned to mediate both drug and natural reward-seeking behaviors. The region is best known as the pallidal output of NAc, receiving significant inputs from both D1- and D2-expressing NAc medium spiny neurons that are altered by repeated cocaine exposure (Creed et al., 2016; Kupchik et al., 2015), and are required for cue+cocaine primed reinstatement (Stefanik et al., 2013b). We and others have shown that VP projections to VTA are especially important for motivated behavior including reinstatement of cocaine seeking (Geisler et al., 2008; Grace et al., 2007; Knowland et al., 2017; Mahler et al., 2014b; Prasad and McNally, 2016; Root et al., 2015; Richard et al., 2016).

VP is characterized by spontaneously active inhibitory projection neurons, and it has long been known to gate VTA neuron activity related to reward and cognition (Fig. 2; Grace et al., 2007; Root et al., 2015; Smith et al., 2009b). Accordingly, inhibiting VP neurons activates VTA DA neurons (Floresco et al., 2003; Grace et al., 2007; Mahler et al., 2014b), while stimulating VP-VTA projections inhibits DA neurons, as well as non-DA VTA neurons (Hjelmstad et al., 2013), allowing VP to bidirectionally control VTA DA neurons via direct or indirect projections. In return, VTA sends DA and non-DA projections back to VP, which participate in memory consolidation and motivation (Stout et al., 2016; Yoo et al., 2016).

VP is crucial for reward-seeking behaviors, and its activity is modulated by salient rewards, reward cues, and punishers in rodents and primates including humans (Haber and Knutson, 2010; Root et al., 2015; Smith et al., 2009b). For example, VP and its projections to VTA and mediodorsal thalamus are essential for cue-elicited seeking of natural rewards, suggesting a role for VP in cue-triggered incentive motivation for natural as well as drug rewards (Ahrens et al., 2016; Chang et al., 2015; Leung and Balleine, 2015; Richard et al., 2016; Smith et al., 2009b). VP is also required for reinstatement of extinguished drug seeking by discrete or contextual cues (Mahler et al., 2014b; Perry and McNally, 2013; Prasad and McNally, 2016; Stefanik et al., 2013b; Wang et al., 2014), stress (McFarland et al., 2004), or cocaine priming injections (Mahler et al., 2014b; McFarland and Kalivas, 2001), indicating that VP is a general mediator of reinstatement regardless of trigger. As discussed above, NAcCo-VP projections are required for cocaine reinstatement, but VP projections back to NAcCo are not similarly necessary (Stefanik et al., 2013b), though these

NAc projections do mediate other forms of natural and drug reward seeking (Smith and Berridge, 2007).

VP is a highly heterogeneous region, and though the implications of such heterogeneity for relapse-related behaviors are still poorly understood, they are intriguing. VP inputs from NAc are anatomically segregated, with NAcCo projecting to a dorsolateral VP subregion, and NAcSh instead projecting to ventromedial VP (Heimer et al., 1991). VP is mostly GABAergic, but glutamatergic, cholinergic, parvalbumin, and other cell types are also present (Geisler et al., 2007; Knowland et al., 2017; Root et al., 2015), the functions of which are largely unknown. Interestingly, some cell types are expressed in different rostrocaudal zones within VP borders, with glutamatergic cells projecting to VTA localized largely in medial and rostral VP, and cholinergic cells being more caudally localized (Geisler et al., 2007; Root et al., 2015), while parvalbumin-expressing neurons are scattered throughout VP (Knowland et al., 2017). These anatomical rostro-caudal differences relate to roles for VP in hedonic/disgust-related behaviors in rodents (Chan et al., 2016; Smith and Berridge, 2005) and humans (Calder et al., 2007; Royet et al., 2016), with caudal VP containing a “hedonic hotspot,” in which stimulation of μ opioid or orexin receptors increases hedonic evaluation of tastes (Ho and Berridge, 2013; Smith and Berridge, 2005). Lesions of this area produce profound anhedonia and aphagia (Cromwell and Berridge, 1993; Smith and Berridge, 2005), and chemogenetic inhibition of caudal VP blocks cocaine-primed, but not cue-induced reinstatement (Mahler et al., 2014b). The rostral half of VP instead appears to mediate cue-triggered or cue-reinforced motivation in particular, since chemogenetic inhibition of rostral VP or its projections to VTA (Fig. 2) attenuates discrete cue-induced cocaine reinstatement without affecting primed reinstatement (Mahler et al., 2014b).

To determine the circuit mechanism by which VP-VTA projections mediate reinstatement, we further examined how rostral VP efferents modulate activity of VTA DA neurons. Contralateral disconnection of rostral VP from VTA DA neurons attenuates cue-induced cocaine seeking, showing that communication between these populations is required (Mahler et al., 2014b). However, the circuit mechanisms by which VP interacts with DA neurons during cued reinstatement remains elusive. Indiscriminate chemogenetic inhibition of VP-VTA projections disinhibited DA neurons *in vivo* and *ex vivo*, confirming the previously reported predominance of GABA in this pathway. This disinhibition of DA neurons is unlikely to explain reductions in cocaine seeking after inhibition of VP afferents though, since VTA disinhibition with a GABA_A antagonist facilitated, rather than attenuated cue reinstatement (Mahler et al., 2014b). We also observed that some fast-firing, short-waveform VTA neurons were *inhibited* upon chemogenetic suppression of VP inputs. It is therefore possible that removing VP GABA inputs disinhibited GABA interneurons, suppressing firing of the recorded VTA DA cells. Another possibility is that chemogenetic inhibition of the glutamatergic component of the VP projection to VTA (~7% of all subcortical glutamate projections to VTA; Geisler and Zahm, 2005) underlies suppression of firing in this subset of recorded VTA neurons. We attempted to test the necessity of this glutamatergic pathway for cue-induced reinstatement of cocaine seeking by disconnecting VP from VTA ionotropic glutamate neurotransmission (unilateral VP chemogenetic inhibition, plus contralateral VTA injection of AMPA/NMDA antagonists), but failed to find

consistent effects of this manipulation in the small group of rats tested (Mahler et al., 2014b). Further investigation of the specific connectivity of VP glutamate versus GABA projections to VTA, and their roles in reinstatement, is therefore warranted.

Beyond revealing the complex roles for VP subregions in drug-seeking behavior, our VP manipulation experiments clearly challenge the intuitive concept that anatomical contiguity (e.g., of the Substance P-delineated VP) represents functional continuity. Recent advances in tools for manipulating genetically- and anatomically-defined pathways *in vivo* have led to a renewed appreciation for such functionally distinct subpopulations of neurons within defined nuclei (e.g., Lenz and Lobo, 2013; Nieh et al., 2013; Stamatakis and Stuber, 2012; Steinberg et al., 2015; Tye and Deisseroth, 2012). In our view, such functional/anatomical heterogeneity likely relates to specific roles played by brain circuits in rodent reinstatement, and potentially in human drug relapse as well.

7. Enhancing face validity of rodent relapse models

Despite the large body of evidence unraveling the neural circuits implicated in cocaine reinstatement in rats, we are far from understanding how these circuits function in human cocaine addiction and relapse. Conventional reinstatement models capture some of the overt characteristics of the addiction/relapse cycle, including voluntary drug use, cessation of drug taking, and resumption of drug use precipitated by similar stimuli to those eliciting relapse in humans. However, many details differ between the situations experienced by experimental animals in these studies and those experienced by recovering addicts, potentially hindering our ability to map circuit/behavior relationships across species (Epstein et al., 2006). Like humans and other primates, rats are sensitive to the contingencies surrounding their drug use, and most will readily cease or greatly reduce their intake when the cost of taking drugs becomes high, or alternative reinforcers are available to pursue instead (Alexander et al., 1981; Belin-Rauscent et al., 2016; Hart et al., 2000; Higgins, 1997; Nader et al., 2008). We highlight two features of addiction in humans that are absent in conventional animal relapse models: 1) presence of alternative reinforcers that may deter drug taking or relapse and 2) negative consequences associated with drug use or relapse.

People usually have many attractive options in life, some of which are mutually exclusive with excessive drug use (e.g., financial security, employment, social relationships). In humans, this idea underlies contingency management, a relatively effective type of treatment for recovering addicts in which drug-free urine can be exchanged for non-drug rewards (e.g., gift cards or money) (Prendergast et al., 2006). In contrast, laboratory rodents typically live in unstimulating environments, frequently in social isolation, and behavioral testing is by far the most engaging thing that happens to them on a regular basis. Recent rodent models have therefore incorporated alternative reinforcers (e.g., palatable food) that are delivered as an alternative to drug, and which can thereby promote voluntary abstinence from drug use. In this way, neural substrates of reinstatement following voluntary abstinence can be probed. For example, Caprioli and colleagues (2015; 2017) trained rats separately to self-administer palatable food pellets and methamphetamine, then subjected them to either forced abstinence from both rewards, or voluntary abstinence from drug due to choice of the food alternative. In this case, both forced- and voluntary-abstinence groups displayed incubation

of methamphetamine craving, and both effects were attenuated by the same pharmacological enhancement of mGluR2 signaling (Caprioli et al., 2015), or activity-selective lesion of dorsomedial striatum neurons recruited during methamphetamine seeking (Caprioli et al., 2017). Venniro et al. (2017) also showed that glutamatergic projections from anterior insular cortex to central amygdala are necessary for cue-induced reinstatement of methamphetamine seeking following voluntary abstinence from “contingency management,” and involvement of this pathway in drug seeking under other conditions should be further studied.

Use of drugs in moderation is nearly ubiquitous in people under socially and legally acceptable circumstances, when the consequences of use are minimal (e.g., having a glass of wine at dinner). Yet there is a subset of individuals in which drug use becomes excessive, and use continues despite mounting consequences. Remarkably, like humans, a subset of outbred rats (usually around 10-25% depending on study conditions) are relatively insensitive to punishment—tolerating shock co-administered with cocaine (Belin et al., 2016; Belin-Rauscent et al., 2016; Vanderschuren et al., 2017), failing to suppress cocaine seeking during a shock-predictive cue (Vanderschuren and Everitt, 2004), or voluntarily crossing an electrified floor to take cocaine (Barnea-Ygael et al., 2012; Cooper et al., 2007). These punishment-resistant rats can be identified based on individual differences in the degree of pre-cocaine voluntary exploration of a novel environment (Belin et al., 2011), impulsivity in the 5-choice serial reaction time task (Economidou et al., 2009), or the pattern of cocaine intake during initial self-administration training (Belin et al., 2009). This indicates that pre-existing individual differences predict the eventual transition from regulated to uncontrolled cocaine seeking in individual animals, a finding which could have major implications for predicting vulnerability to addiction and relapse in humans. We refer readers to recent excellent reviews for more information about the characteristics and neural substrates of punished drug intake (Belin-Rauscent et al., 2016; Vanderschuren et al., 2017).

Of note, cocaine experience can reduce the ability of people (Ersche et al., 2016) or rats (Simon et al., 2009; Wied et al., 2013) to properly use negative outcomes to guide their subsequent behavior. Although punishing drug use criminally, with taxation, or even with advertising (e.g., placement of graphic, aversive photos on cigarette packages) is somewhat effective at reducing drug use (Milton and Everitt, 2012), drug-induced insensitivity to punishment may sabotage these efforts in established addicts (Ersche et al., 2016). Given these facts, some labs have begun incorporating negative outcomes of drug use into preclinical relapse models. For example, the Yavin Shaham laboratory developed a cue/context reinstatement model in which abstinence is self-imposed by rats due to co-administration of footshock with drug after initial punishment-free training (Marchant et al., 2013a, 2013b; Pelloux et al., 2017; Venniro et al., 2016). In this approach, rats are trained to lever press for drug and a discrete cue in Context A (self-administration context with distinct visual and olfactory cues), then are introduced to Context B (punishment context) where lever pressing produces not only drug and discrete cues (tone+light), but also footshock coincident with 50% of drug/cue deliveries. Initial punishment training features a weak (0.3mA) footshock, and the intensity of shock is increased across training until pressing ceases in all rats (up to 1mA). Importantly, when shocks are delivered in a non-contingent manner in Context B, drug intake is not suppressed, showing that motivation to avoid punishment, rather than shock-induced stress alone, suppresses drug (alcohol) seeking

(Marchant et al., 2013a). Following self-imposed footshock-induced abstinence, rats are reintroduced to Context A in the absence of drug. As expected, drug seeking in the punishment context is low even when discrete tone/light cues are delivered upon lever pressing, yet the same cues elicit robust reinstatement when delivered in Context A where unpunished drug was delivered (Krasnova et al., 2014).

We have recently modified Marchant and colleagues' punishment-induced abstinence approach (Marchant et al., 2013a) for use with cocaine (similar to Pelloux et al., 2017), and characterized Long-Evans rats' cocaine seeking during self-administration and voluntary abstinence (Fig. 3A; unpublished observations). As previously reported, rats showed marked variability in punishment resistance (Chen et al., 2013; Deroche-Gamonet et al., 2004; Marchant et al., 2014), with ~16% displaying significant resistance to punishment under this relatively mild shock intensity (Fig. 3B). When we examined the specific behaviors exhibited by rats during shock-punished training, most rats displayed "stretch and attend" hesitations following each shock delivery, a typical rodent risk assessment behavior (Blanchard et al., 2011), which here may reflect a mixed motivational state in which motivation to seek cocaine competes with motivation to avoid shock (Fig. 3C). Hesitations consisted of the rats stretching their forequarters toward the active lever and sometimes touching it (Fig. 3D), before withdrawing the forepaw rapidly without depressing the lever. Hesitations were most prevalent in the most punishment sensitive rats, and was less common in those who continued to take cocaine despite being shocked. Therefore, hesitations could be used as an objective measure of "mixed motivation" to receive cocaine in punishment sensitive rats. We also noticed that numerous rats shifted their lever pressing behavior to the unreinforced/unpunished inactive lever during punishment training (Fig. 3A), potentially representing diversion of cocaine seeking into exploration of alternate, less risky strategies to obtain cocaine. Inactive lever pressing, in addition to hesitations, could therefore be used to quantify mixed motivations in such studies.

To date, few differences in relapse circuits following experimenter-imposed versus voluntary abstinence have been demonstrated. We predict that further study with these new self-imposed abstinence models will reveal such differences based on abstinence method and other behavioral circumstances, however. For example, we predict that fear- and aversion-related regions will be recruited during abstinence due to punishment avoidance, but not due to choice of an alternative reinforcer, experimenter-imposed abstinence, or extinction training. In sum, we believe that attention must be paid to maximizing the similarity of rodent relapse models to human behavior in addiction. This may inform our understanding of the genetic or environmental factors that cause individual differences in relapse vulnerability, and the precise neural circuits mediating decisions to take or abstain from drugs.

8. Conclusions

Cocaine relapse is a deceptively complex phenomenon, engaging a variety of brain circuits that vary due to experimental details of animal studies that are often glossed-over. In other words, the devil is in the details when it comes to identifying cocaine relapse circuits. Instead of despairing this frustrating fact, we hope that by improving preclinical models to

more faithfully emulate conditions under which humans take drugs, decide to quit, and then relapse, this will facilitate our identifying the specific circuits underlying relapse risk in individual humans. This conceptual shift could facilitate development of individualized therapeutic strategies targeting aberrant activity in the circuits most relevant to an individual's most problematic relapse risk factors (McKay et al., 1996; Moeller and Paulus, 2018). However, we must first understand how neural circuits function during *clinically-relevant* cocaine-seeking behaviors, and how these systems are hijacked with repeated drug use. Fortunately, modern neuroscience tools for imaging and manipulating circuit activity *in vivo* hold great promise for doing so, both by characterizing neural circuits underlying complex relapse-related behaviors in rodents, and perhaps for one day intervening in these circuits to selectively treat psychiatric disorders like addiction in humans.

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Abbreviations

| | |
|---------------|--|
| AMPA | α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid |
| BLA | basolateral amygdale |
| BNST | bed nucleus of the stria terminalis |
| CeA | central amygdala nucleus |
| CRF | corticotropin-releasing factor |
| DA | dopamine |
| D1 | dopamine receptor 1 |
| D2 | dopamine receptor 2 |
| GABA | γ -Aminobutyric acid |
| ILC | infralimbic cortex |
| i.c.v. | intracerebroventricular |
| LTN | laterodorsal tegmental nucleus |
| LH | lateral hypothalamus |
| mPFC | medial prefrontal cortex |
| mGluR | metabotropic glutamate receptor |
| NMDA | N-methyl-D-aspartate |
| NE | norepinephrine |

| | |
|--------------|------------------------------------|
| NAc | nucleus accumbens |
| NAcCo | nucleus accumbens core |
| NAcSh | nucleus accumbens shell |
| OFC | orbitofrontal cortex |
| OX1R | orexin receptor 1 |
| PLC | prelimbic medial prefrontal cortex |
| PVT | paraventricular thalamus |
| VP | ventral pallidum |
| VTA | ventral tegmental area |
| 5HT | 5-hydroxytryptamine |

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Highlights

- Rodent reinstatement experiments may effectively model human cocaine relapse
- Details of such models influence the neural circuits engaged during cocaine seeking
- We summarize common rat models, and neural circuits involved
- We also summarize strategies for increasing face validity of these models
- Such studies could help identify relapse risk factors in individual addicted humans

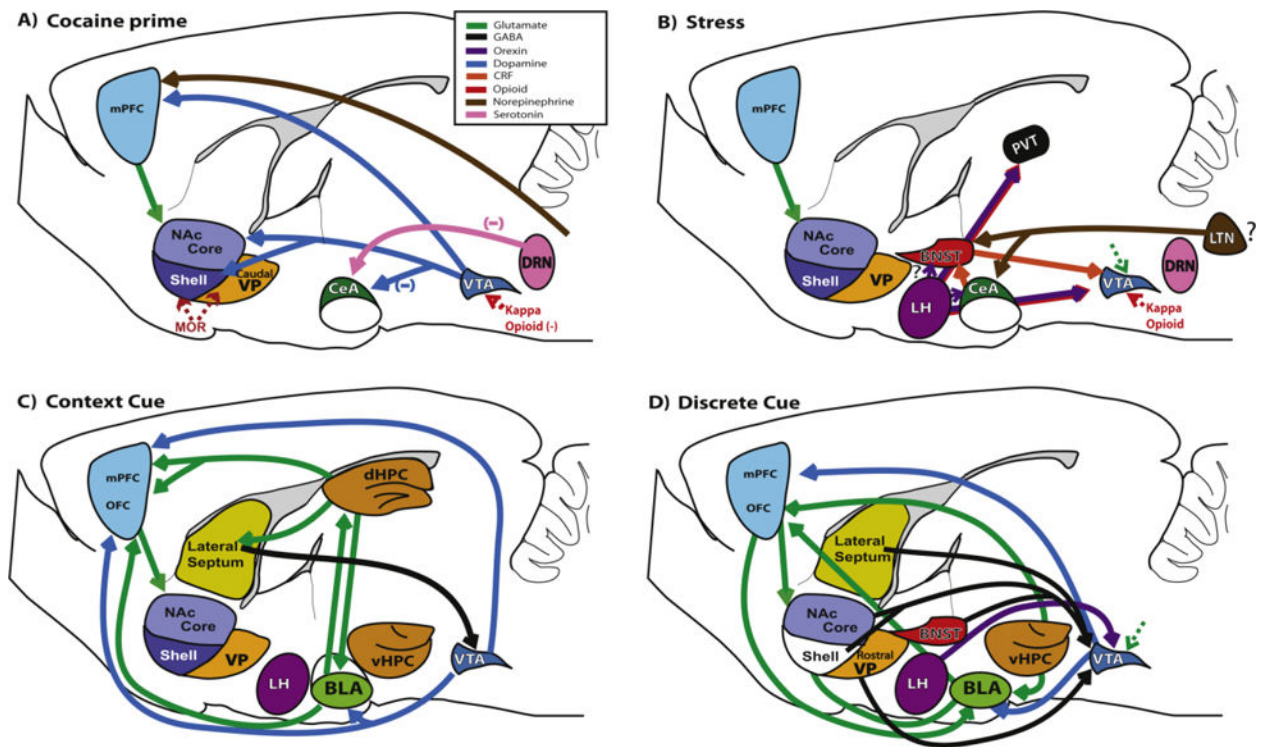


Figure 1. Key neural circuits underlying different types of cocaine reinstatement behavior
 Overlapping, but distinct neural networks mediate reinstatement behavior elicited by different classes of relapse triggers including A) cocaine priming, B) stress, C) discrete cues, and D) context cues. See text for references of specific findings and abbreviations. BLA: basolateral amygdala; BNST: bed nucleus of the stria terminalis; CeA: central amygdala nucleus; CRF: corticotropin-releasing factor; dHPC: dorsal hippocampus; DRN: dorsal raphe nucleus; LTN: laterodorsal tegmental nucleus; LH: lateral hypothalamus; mPFC: medial prefrontal cortex; NE: norepinephrine; NAc: nucleus accumbens; NAcCo: nucleus accumbens core; NAcSh: nucleus accumbens shell; OFC: orbitofrontal cortex; PVT: paraventricular thalamus; vHPC: ventral hippocampus; VP: ventral pallidum; VTA: ventral tegmental area

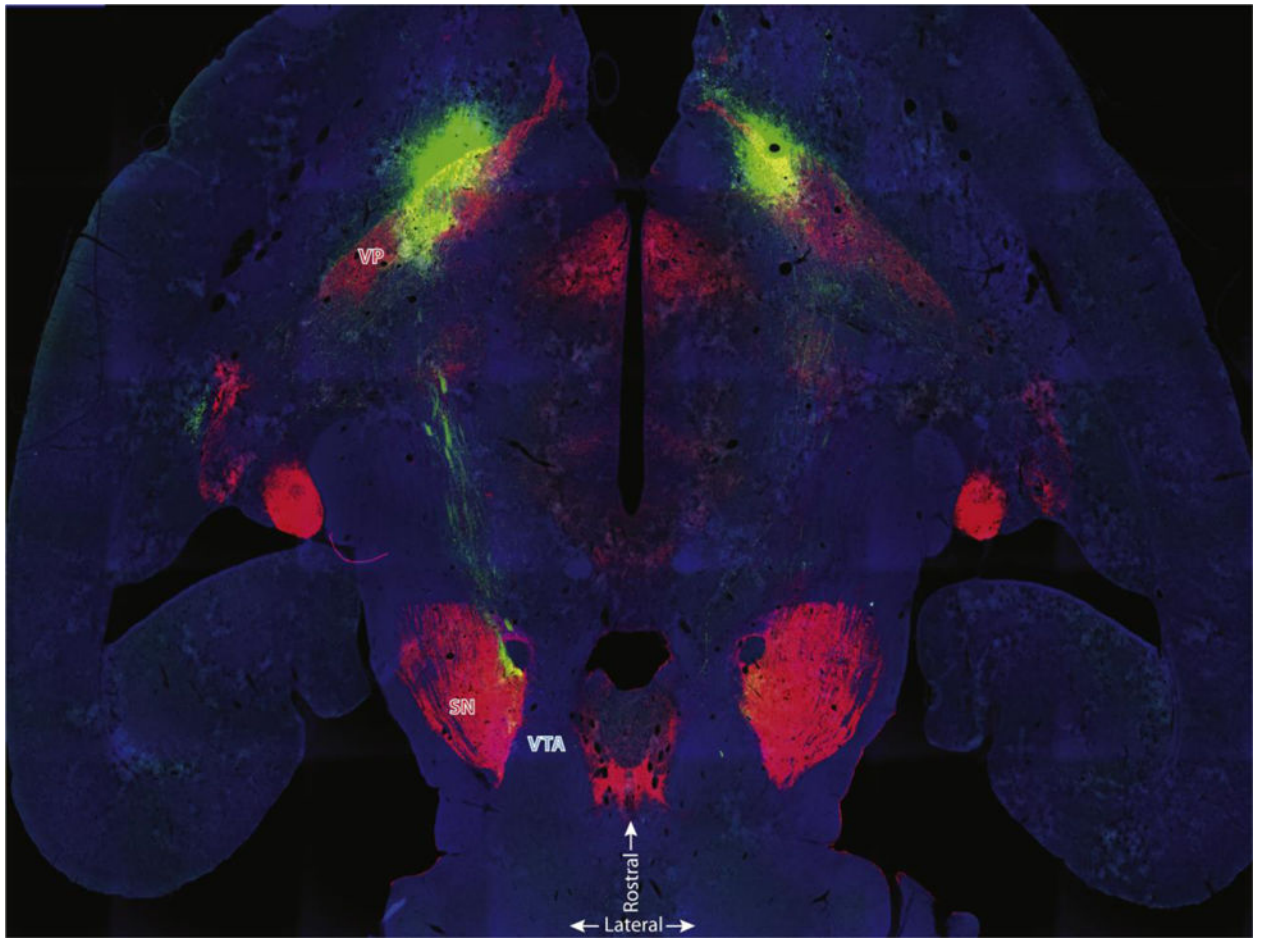


Figure 2. Ventral pallidum projection to ventral tegmental area

Immunofluorescent visualization of Substance P (red; defining VP borders), green fluorescent protein (green; defining expression of viral-tagged neurons in VP and immediately adjacent regions, and their axons), and tyrosine hydroxylase (blue; defining dopamine neurons in VTA), in a horizontal view.

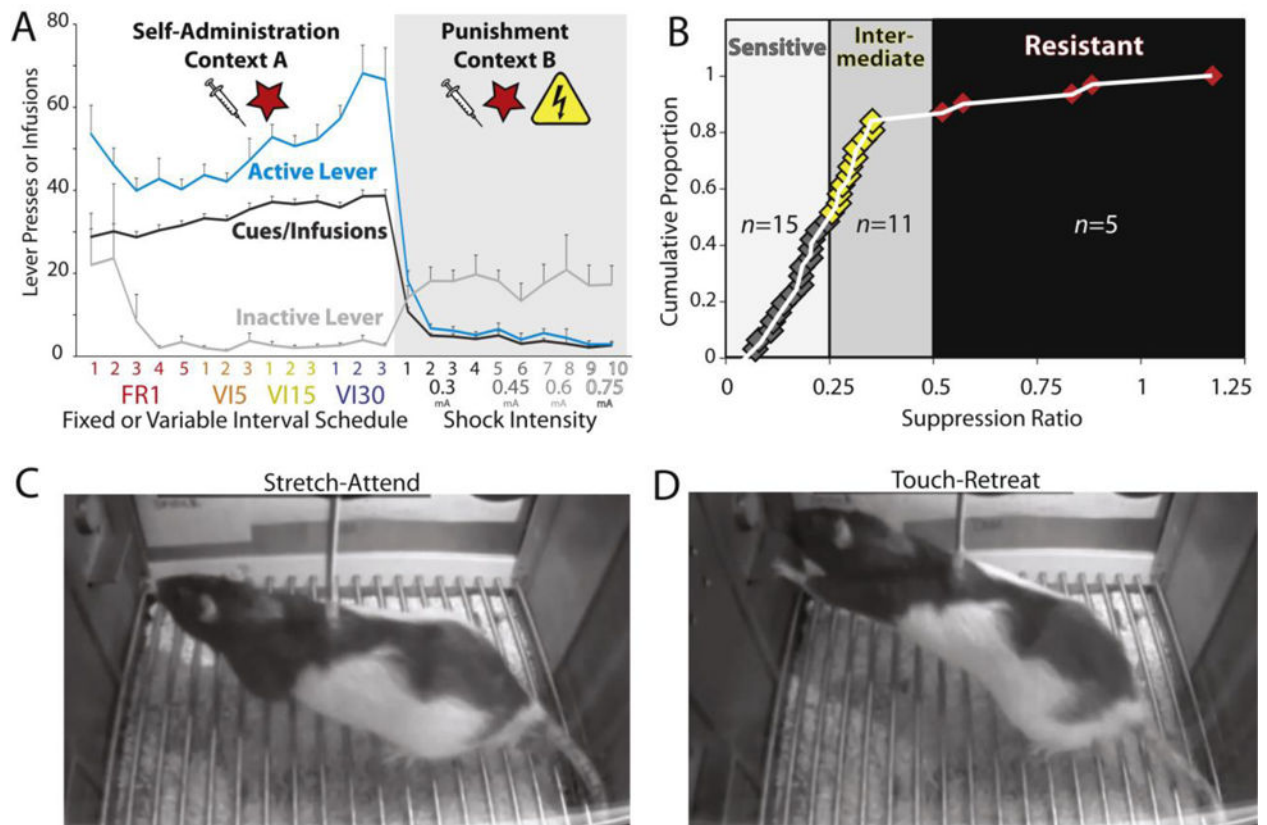


Figure 3. Voluntary Abstinence From Cocaine Via Punishment

A) Cocaine self-administration behavior in Context A, followed by suppression of cocaine seeking in Context B, where lever presses yield cocaine and cues, but also shock on 50% of trials. Shock intensity was increased from 0.3-0.75mA over subsequent punishment training, until all rats voluntarily ceased pressing. B) During the punishment phase in Context B, rats varied in their sensitivity to shock for suppressing cocaine self-administration. Suppression ratio is defined as the decrease in pressing on punishment day 1, relative to infusions self-administered on the last day of unpunished self-administration [infusions on punishment day 1/infusions on last self-administration day; Y-axis indicates cumulative proportion of sampled rats, with 1 indicating 100% of tested rats (Pelloux, et al 2007)]. Most rats showed high (n=15) or intermediate (n=11) sensitivity to shock, while 16% (n=5) were resistant to punishment in this sample. During the punishment phase, rats showed putative indices of mixed motivational states, namely C) stretch-attend, and D) touch-retreat behaviors.