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Review

How contexts promote and prevent relapse to drug seeking

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The contexts where drugs are self-administered play an important role in regulating persistent drug taking and in relapse to such taking after periods of abstinence. Here, we review the behavioral and brain mechanisms enabling contexts to promote and prevent relapse to drug seeking. We review the key brain structures, their neuropharmacology and their connectivity. We discuss the similarities and differences between the mechanisms for context-induced reinstatement of drug seeking vs. other forms of relapse to drug seeking in animal models and we highlight the numerous deficits in our understanding. We emphasize that current understanding, although significant, defies explanations in terms of models at the level of brain structures and their connectivity. Rather, we show that there is significant functional compartmentalization and segregation within these structures during reinstatement and extinction of drug seeking that parallels their anatomical segregation into circuits and channels. A key challenge is to recognize this complexity, understand how these circuits and channels are organized, as well as understand how different modes of activity of ensembles of neurons within them promote abstinence or relapse to drug seeking.

Keywords: Accumbens, addiction, amygdala, circuits, context-induced reinstatement, learning, orexin, prefrontal cortex, reinstatement, relapse, renewal

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Drug addiction remains a chronic condition imposing significant burdens on individuals, their families and communities. It is associated with increased rates of physical health problems including cardiovascular and liver disease; mental health problems including depression and anxiety; reduced levels of productivity, as well as higher utilization of health and social services (Lim *et al.* 2012; Nutt *et al.* 2010; Rehm *et al.* 2009). Considerable progress has been made in understanding the mechanisms of drug addiction including those contributing to the reinforcing effects of drugs of abuse and the escalation as well as loss of control over drug intake rendering it compulsive. A fundamental problem is relapse to drug taking after a period of abstinence. Rates of relapse are high and largely unchanged over a long period of time (Conklin & Tiffany 2002; McLellan *et al.* 2001), even allowing for differences in clinical outcome measures used across studies. Moreover, even though agonist-based therapies (Negus & Henningfield 2015), opioid antagonists (Connor *et al.* 2016) and behaviorally based contingency management techniques (Gupta 2015) are efficacious in some individuals with addictions, there are few other truly efficacious pharmacological and behavioral tools available to clinicians and individuals with addictions to combat relapse and maintain abstinence.

Basic work in neuroscience has provided significant information on the behavioral and brain mechanisms that initiate and sustain behavioral change. The relevance and importance of this work to the clinical problem of relapse is rightly judged on its clinical impact (Connor *et al.* 2016; Hall *et al.* 2014). There have been some successes, but much of this basic work is yet to achieve translational success (Heilig *et al.* 2016). There are many reasons for this but one theme that we explore here is that the mechanisms for behavioral change during extinction and reinstatement are significantly more nuanced than most current models of relapse to drug seeking allow. Here, we review current knowledge on how contexts promote and prevent relapse to drug seeking. The contexts where drugs are self-administered play an important role in regulating persistent drug taking and in relapse to such taking after periods of abstinence. Our focus is on the role of contexts, but we consider evidence from other models of relapse to drug seeking where that evidence helps highlight similarities and differences between the mechanisms for context-induced vs. other forms of relapse to drug seeking. We also highlight several deficits in our understanding of how these circuits act to promote or prevent relapse to drug seeking.

Behavioral mechanisms of context-induced reinstatement

The role of contexts in promoting and preventing relapse to drug taking is best exemplified by the phenomenon of 'renewal' or context-induced reinstatement. Renewal is the term used to describe recovery of extinguished behavior with a change in context (Bouton & Bolles 1979). Typically,

subjects are trained to respond for a reward in one context, context A. This responding is then extinguished in a second context, context B. When tested in context B, reward seeking is low (i.e. it has been extinguished). However, when tested in context A, reward seeking returns (i.e. it has been renewed). The first demonstration of renewal of drug seeking was provided by Crombag and Shaham (2002), who reported the ABA renewal of responding for speedball (heroin + cocaine) in rats. It has been shown for instrumental responding based on other reinforcers, including natural rewards such as food pellets (Nakajima 2000) or liquid sucrose (Hamlin *et al.* 2006) as well as drug rewards such as alcohol (Hamlin *et al.* 2007; Marinelli *et al.* 2007; Zironi *et al.* 2006), cocaine (Crombag *et al.* 2002; Fuchs *et al.* 2005), heroin (Bossert *et al.* 2004), nicotine (Diergaarde *et al.* 2008) and methamphetamine (Rubio *et al.* 2015). Renewal is called 'context-induced reinstatement' in the drug seeking and relapse literature (Crombag *et al.* 2008). The reasons for this are beyond the scope of the review; however, we use both terms interchangeably here.

Renewal shows that extinction is context specific and that it is lost with a change in context between extinction and test. This provides evidence that extinction is not simply an erasure of drug seeking, but additionally involves imposition of a mask on drug seeking which reduces drug seeking in the extinction context but not elsewhere (Bouton 2002). Removal of this mask by context change is a major source of relapse after behavior change (Bouton 2002; Conklin & Tiffany 2002).

Until recently, the nature of this mask and the mechanisms for context-induced reinstatement of drug seeking and instrumental responding more generally were unknown. The assumption was that these were similar to those involved in renewal of Pavlovian conditioning. In renewal of Pavlovian conditioning, a rat is exposed to pairings of a conditioned stimulus (CS) and an unconditioned stimulus in a distinctive context (A). Responding to the CS is then extinguished in a second, different context B via presentations of the CS alone. Under these conditions, the conditioned response to the CS generalizes well from the training to extinction context and then declines, reflecting formation of the extinction association. The extinction context serves to gate retrieval of the extinction association so that this association is retrieved only when the animal is tested in the extinction context (ABB), but not elsewhere (Bouton 2002). So, renewal of responding to the CS is observed when the animal is tested in the training context (ABA renewal), a third context (ABC renewal), or in a second context after training and extinction in the same context (AAB renewal).

Work by Todd, Bouton and co-workers has shown that extinction of instrumental learning is different from extinction of Pavlovian learning. Todd and Bouton first showed that each of the three major forms of renewal, ABA, ABC and AAB, can be observed for instrumental responding for natural reinforcers (Bouton & Todd 2014; Bouton *et al.* 2011; Todd 2013; Todd *et al.* 2014). This is important because earlier work with drug reinforcers could detect ABA but not other forms (e.g. AAB) of renewal (Bossert *et al.* 2004; Crombag & Shaham 2002; Fuchs *et al.* 2005). It is now clear that at least one reason for this is that animals must be trained on an instrumental

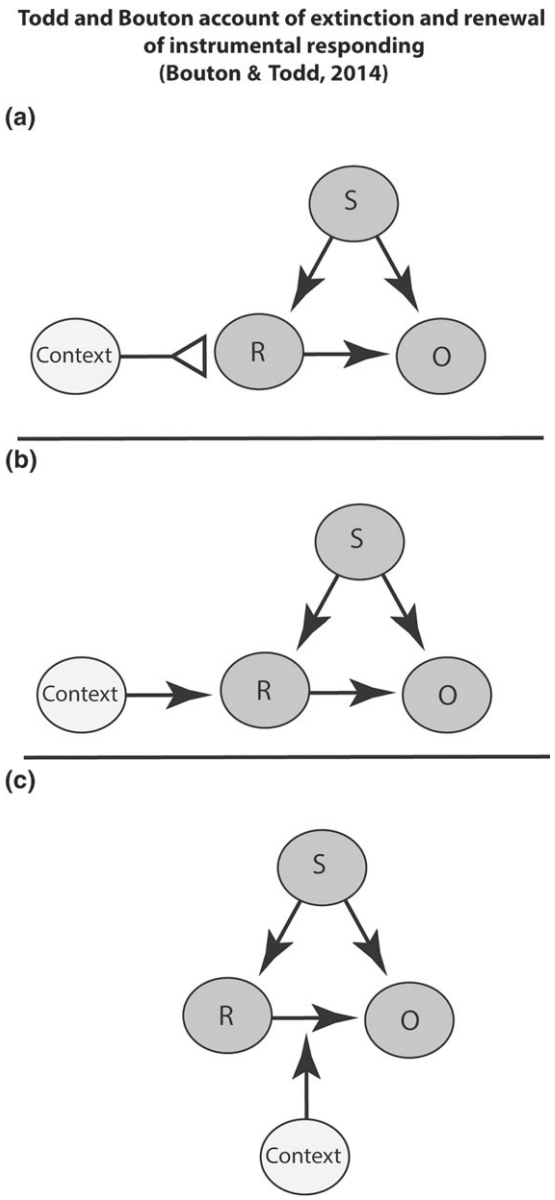

Figure 1: The associative structures for extinction and context-induced reinstatement of instrumental responding. (a) During extinction, the context forms a direct inhibitory association with the response. (b) During context-induced reinstatement, the context can control responding via a direct excitatory association with the response or (c) by gating the association between the response and its outcome.

response in the test context in order to be reliably observed for these other forms of reinstatement (AAB and ABC).

Next, Todd and Bouton were able to isolate the mechanism for extinction of instrumental learning (Fig. 1). In instrumental learning, animals form associations between the response (e.g. lever press), the outcome (e.g. food) as well between the various discrete cues that may accompany this training. Todd and Bouton showed that extinction of

instrumental learning occurs because the extinction context forms an inhibitory association with the instrumental response (Rescorla 1993, 1997; Todd 2013; Todd *et al.* 2014) (Fig. 1). This is different from Pavlovian conditioning where the context acts to gate retrieval of an extinction association. This is a fundamental discovery relevant to understanding the brain circuits for extinction and reinstatement of drug seeking. Responding is low at the end of extinction training, and when the animal is later tested in the extinction context, because the context acts directly to inhibit the drug-seeking response. Removing the animal from this context releases responding from this inhibition and yields renewal if a previously trained instrumental response is available in the test context. This core psychological difference in the behavioral mechanisms typical for extinction of Pavlovian and instrumental conditioning implies that the brain mechanisms for extinction of these two forms of learning will likely be more different than they are similar, a possibility not widely recognized.

The associative structure that mediates responding during renewal/context-induced reinstatement of drug seeking, i.e. the psychological mechanism for relapse, remains poorly understood. Studies of non-drug rewards show that context–reward associations are not critical for renewal of instrumental responding (Todd 2013). Bouton and Todd (2014) have noted that contexts can and do serve multiple roles in instrumental learning. They can and do control responding during renewal directly via a context–response–outcome association and indirectly via gating a response–outcome association (Fig. 1). Both of these mechanisms allow contextual control over instrumental responding and support high levels of responding during context-induced reinstatement. It appears reasonable to assume that similar processes characterize context-induced reinstatement of drug seeking. However, this remains to be shown and is an important direction for further research. Of additional interest will be the relationship between contextual control over extinction and reinstatement of drug seeking and the brain mechanisms allowing Pavlovian stimuli to guide action and invigorate instrumental responding. Studies of instrumental learning have shown both general, response invigorating effects (general Pavlovian to instrumental transfer) and outcome-specific enhancements (specific Pavlovian to instrumental transfer) of reward predictive cues on instrumental responding for a reward. These general and specific transfer effects have dissociable amygdala striatal and pallidal substrates (Corbit & Balleine 2015). Although the experimental procedures for studies of extinction and reinstatement differ considerably from those of studies of transfer, the brain regions frequently implicated in renewal of drug seeking, and reviewed here, overlap considerably with those implicated in specific transfer whereas those brain regions most frequently implicated in cue- or priming-induced reinstatement overlap with those for general transfer.

Prefrontal cortex

One of the most influential models of the brain mechanisms for reinstatement of drug seeking is that distinct neural circuits emerging from dorsal vs. ventromedial prefrontal cortex (vmPFC) contribute to the reinstatement and extinction of drug seeking. Specifically, the prelimbic (PL) region is implicated in reinstatement of drug seeking and the infralimbic (IL) region is implicated in extinction of drug seeking (Kalivas & Volkow 2005; Peters *et al.* 2008, 2009). According to this model, a PL→accumbens core (AcbC)→ventral pallidum (VP) pathway is obligatory for reinstatement of drug seeking, whereas an IL→accumbens shell (AcbSh) pathway is obligatory for the expression of extinction of drug seeking. This model has served as a useful heuristic to parse the brain mechanisms promoting and preventing relapse to drug seeking. Moreover, these opposing roles for the mPFC in reinstatement vs. extinction are consistent with broader roles for these regions in the extinction and reinstatement of other forms of learning (Quirk *et al.* 2006) and models of prefrontal function (Gourley & Taylor 2016). So, return to the training context, in a typical context-induced reinstatement experiment, should recruit PL PFC and associated circuits to cause reinstatement, whereas return to the extinction context should recruit IL PFC and associated circuits to inhibit responding.

In the case of drug seeking, much of the evidence for this dichotomy of prefrontal function rests on the contrasting effects of manipulations of PL and IL on expression of reinstatement or extinction of drug seeking. For example, McFarland and Kalivas (2001) showed that inactivation of PL via the γ-aminobutryic acid (GABA) agonists baclofen/muscimol or infusions of the dopamine receptor antagonist fluphenazine prevented primed reinstatement of cocaine seeking. This role for PL is robust, including but not limited to, cue-induced reinstatement of cocaine seeking (McLaughlin & See 2002), stress-induced reinstatement of cocaine (Capriles *et al.* 2003) or high-fat food (Calu *et al.* 2013) seeking and cue-induced reinstatement of methamphetamine seeking (Rocha & Kalivas 2010). Importantly for the present purposes, it extends to context-induced reinstatement of cocaine (Fuchs *et al.* 2005) and alcohol (Willcocks & McNally 2013) seeking. It has also been observed for context-induced reinstatement of seeking a food reinforcer (Eddy *et al.* 2016). These findings support the claim that PL PFC may be part of a final common pathway for reinstatement of drug seeking. However, several other findings are not consistent with this notion (Moorman *et al.* 2015). For example, reversible inactivation of PL does not prevent context-induced reinstatement of heroin seeking (Bossert *et al.* 2011), despite PL contributing to both cue and heroin priming-induced reinstatement of heroin seeking (Rogers *et al.* 2008; See 2009).

Conversely, Peters *et al.* (2008) first reported that inactivation of IL prevented expression of extinction of cocaine seeking, a role that depended on interactions with AcbSh (see below). This role for IL in extinction of drug seeking depends on glutamatergic and β-adrenergic signaling (LaLumiere *et al.* 2010) and can be enhanced by positive allosteric modulation of IL function (LaLumiere *et al.* 2012). This role for IL has also been observed for extinction of responding for a food reinforcer (Eddy *et al.* 2016). However, others have reported opposing or no effects of IL manipulations on extinction of drug seeking. For example, IL inactivation attenuates cue- and drug-induced reinstatement of heroin

seeking (Rogers *et al.* 2008), cue-induced reinstatement of methamphetamine seeking (Rocha & Kalivas 2010), context-induced reinstatement of heroin seeking (Bossert *et al.* 2011) and has no effect on the extinction of alcohol seeking (Willcocks & McNally 2013).

Thus, there is mixed evidence for a PL/IL dichotomy in controlling reinstatement vs. extinction of drug seeking and the strongest evidence is derived from studies of cocaine seeking with evidence from other drug reinforcers mixed (Moorman *et al.* 2015). The reasons for these discrepancies are unclear and have been considered extensively by others (Gourley & Taylor 2016; Moorman *et al.* 2015). A better understanding of the organization and function of corticostriatal circuits will be central to resolving these discrepancies. Indeed, the role of IL in extinction of drug seeking is most closely associated with projections to AcbSh, whereas the role of PL in reinstatement is most closely associated with projections to AcbC (Peters *et al.* 2008, 2009).

However, we argue that a more nuanced analysis is necessary to address these inconsistencies and yield a deeper understanding of the role of PFC and the circuits of which it is a part in promoting and preventing relapse to drug seeking. There are a variety of ways of parsing prefrontal circuits and function based on distinct cell types, connectivity and activity. For example, neurons from both PL and IL project extensively throughout the ventral striatum, with clear differences in patterns of innervation not mapping readily onto anatomical boundaries there (Berendse *et al.* 1992; Heidbreder & Groenewegen 2003; Mailly *et al.* 2013). Moreover, within an individual corticostriatal pathway defined on classic anatomical boundaries, such as the IL→AcbSh pathway, there are important differences. Different IL neurons target distinct AcbSh compartments that, in turn, target distinct hypothalamic, pallidal and thalamic regions (Thompson & Swanson 2010) that have been differentially implicated in promoting vs. preventing appetitive motivation or reinstatement of drug seeking. So, small differences in connectivity within this single IL→AcbSh corticostriatal pathway map onto diverse and distinct downstream targets. A key insight into the organization of these circuits and their roles in reinstatement comes from recent studies from the Hope Laboratory. Warren *et al.* (2016) mapped the population of IL neurons recruited during exposure to context recently associated with food seeking or recently associated with extinction of food seeking and showed that only a small number of IL neurons were recruited during each. Then, using the Daun02 inactivation method which allows selective lesioning of neurons based on their activity status (Cruz *et al.* 2013), they showed that food seeking could be reduced or increased depending on whether the ensembles recruited during exposure to the food seeking or extinction context were inactivated. Moreover, global reversible IL inactivation via infusions of GABA agonists had no significant effect. It is therefore likely that the relevant level of analysis is through ensembles of prefrontal neurons and the specific circuits and channels in which they are located rather than classical anatomical boundaries such as PL and IL (Fig. 2).

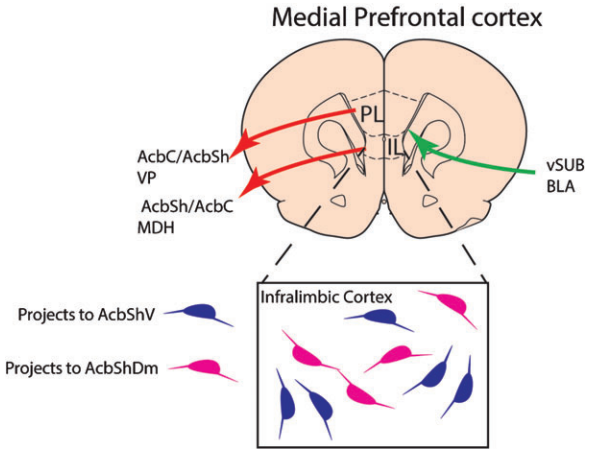

Figure 2: The Prefrontal cortical regions, as well as some of their major afferents and efferents, implicated in reinstatement and extinction of drug seeking. Although a functional dichotomy between PL (promoting reinstatement) and IL (promoting extinction) has been observed in some studies, this is not consistently supported by the literature. The roles of different PFC cell types, as well as distinct corticostriatal circuits emerging from within individual PFC regions, remain poorly understood.

Hippocampus

Unsurprisingly, given the role of context, the hippocampus serves an important role in context-induced reinstatement of drug seeking (Fig. 3). Hippocampus, especially CA3, is recruited during context-induced reinstatement to cocaine seeking (Marinelli *et al.* 2007). Fuchs *et al.* (2005) reported that reversible inactivation of dorsal hippocampus (DH) via infusions of tetrodotoxin prevented context-induced reinstatement of cocaine seeking. Likewise, Luo *et al.* (2011) reported that dorsal hippocampal inactivation, targeting the CA3 subregion, prevented context-induced reinstatement of cocaine seeking. The actions of dopamine at D1 receptors (Xie *et al.* 2014) and glutamate at $mGluR_1$ (Xie *et al.* 2010) as well as NR2-expressing *N*-methyl-D-aspartate receptors (Xie *et al.* 2013) have all been shown to be important for DH contributions to context-induced reinstatement. The role of DH in context-induced reinstatement of seeking other drugs is underexplored.

This DH contribution to context-induced reinstatement depends, in part, on basolateral amygdala (BLA). There are serial interactions between BLA and DH, because pharmacological disconnection of these regions prevents context-induced reinstatement of cocaine seeking (Fuchs *et al.* 2007); however, the nature of this interaction remains to be determined. This DH contribution also appears to depend on a circuit reaching ventral tegmental area (VTA) via lateral septum (LS). Using transsynaptic tracing, Luo *et al.* (2011) identified a CA3→LS→VTA circuit that was independent of the previously reported VTA pathway originating from ventral subiculum (vSUB) and then showed that reversible inactivation of CA3, or disconnection of the LS→VTA pathway prevented context-induced reinstatement of cocaine seeking.

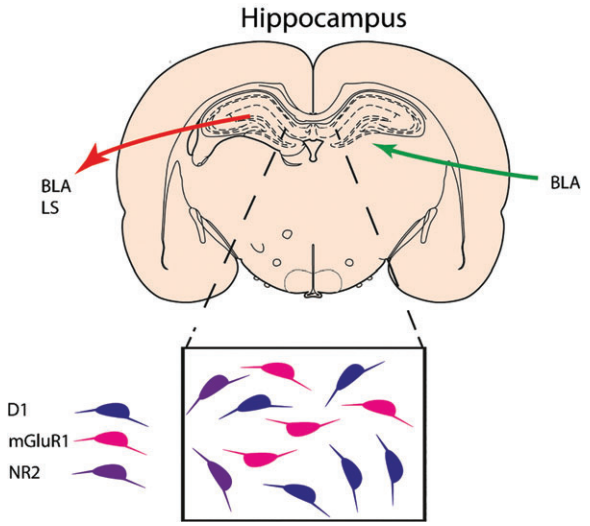

Figure 3: The Hippocampus, both dorsal and ventral, contributes to context-induced reinstatement. This is due, in part, to dorsal hippocampal connectivity with BLA as well as LS. Although some critical neurotransmitter and receptor families have been identified for this role, little is otherwise known about hippocampal contributions to extinction or context-induced reinstatement of drug seeking.

The vSUB serves a well-documented role in context-induced reinstatement. Theta burst stimulation of vSUB induces reinstatement of extinguished cocaine seeking (Vorel *et al.* 2001), and reversible vSUB inactivation prevents context-induced reinstatement of cocaine (Lasseter *et al.* 2010b) or heroin (Bossert & Stern 2012) seeking. This role extends to context-induced reinstatement following punishment-imposed abstinence from alcohol seeking (Marchant *et al.* 2016). The circuitry for this vSUB contribution to context-induced reinstatement is only beginning to be understood but involves, at least in part, vSUB projections into the AcbSh (see below). The roles of other vSUB projections remain to be determined. For example, Bossert *et al.* (2016) detected significant recruitment of the vSUB→dorsomedial PFC (dmPFC) pathway during context-induced reinstatement of heroin seeking, but pharmacological disconnection of this pathway had no effect on reinstatement.

Basolateral amygdala

The BLA (Fig. 4) is consistently recruited during context-induced reinstatement of alcohol (Hamlin *et al.* 2007; Marinelli *et al.* 2007), sucrose (Hamlin *et al.* 2006) or cocaine (Hamlin *et al.* 2008) seeking. The role of BLA in context-induced reinstatement is upstream of dopamine actions at D1 dopamine receptors because systemic administrations of a D1 dopamine receptor antagonist do not prevent recruitment of BLA during context exposure but do prevent reinstatement (Hamlin *et al.* 2007). Context-induced reinstatement of cocaine seeking can be prevented by reversible BLA inactivation (Fuchs *et al.* 2005) and context-induced reinstatement of alcohol seeking by microinjections of an opioid receptor antagonist (Marinelli *et al.* 2010). Thus, converging lines of evidence implicate BLA in this reinstatement. Moreover, BLA contributes to other forms of reinstatement of drug seeking including cue-induced reinstatement of cocaine seeking (Stefanik 2014) and cue- or heroin-primed reinstatement of heroin seeking (Fuchs & See 2002; Rogers *et al.* 2008), among others.

Much remains to be learned about BLA contributions to reinstatement of drug seeking. The specific BLA cell type(s), the nature of learning-related plasticity in these BLA neurons and their relationship to reinstatement, as well as the precise circuitry in which BLA sits all require further study. As noted previously, pharmacological disconnections show serial interactions between DH and BLA in context-induced reinstatement of cocaine seeking (Fuchs *et al.* 2007). These disconnections of BLA from orbitofrontal (Lasseter *et al.* 2010a) and dmPFC (Fuchs *et al.* 2007) also reduce context-induced reinstatement of cocaine seeking but ipsilateral disconnection of these same regions has the same effect, suggesting complex interactions between these regions in reinstatement. The role of other major BLA projections, including to ventral striatum, remain to be determined. However, optogenetic inhibition of either the BLA→AcbC or BLA→PL PFC pathway is sufficient to reduce cue-induced reinstatement of cocaine seeking (Stefanik 2014).

The compartmentalization of BLA circuits controlling extinction and context-induced reinstatement of drug seeking, as well as appetitive motivation more generally, requires more investigation. It is now well established that during emotional learning and responding the activity of the primary BLA output neurons – glutamatergic principal neurons – are subject to complex regulation by different classes of GABAergic interneurons (Wolff *et al.* 2014). There is also renewed interest in anatomical- and functional-based segregation of BLA output circuits (Beyeler *et al.* 2016; Janak & Tye 2015) and these have been shown to influence extinction and reinstatement in other learning preparations (Herry *et al.* 2008; Senn *et al.* 2014). The extensive collateralization of BLA output pathways (Shinonaga *et al.* 1994) makes these analyses difficult, but we know little about the specific BLA cell types and their organizations that are relevant to understanding reinstatement. These will be important for understanding how BLA contributes to reinstatement and extinction of drug seeking. There is also anatomical and functional segregation along the rostral-caudal axis of BLA. For example, caudal parts of BLA target different ventral striatal compartments than do more rostral parts of BLA (Cho *et al.* 2013; McDonald 1991). There have been several reports that pharmacological manipulations of rostral and caudal BLA (cBLA) have different effects on behavior and appetitive motivation (Jean-Richard Dit Bressel & McNally 2015; Kantak *et al.* 2002; McLaughlin & Floresco 2007). Of relevance here, cBLA but not rostral BLA has been identified as an important factor for both the acquisition (McLaughlin & Floresco 2007) and expression (Millan & McNally 2011) of extinction of instrumental responding for

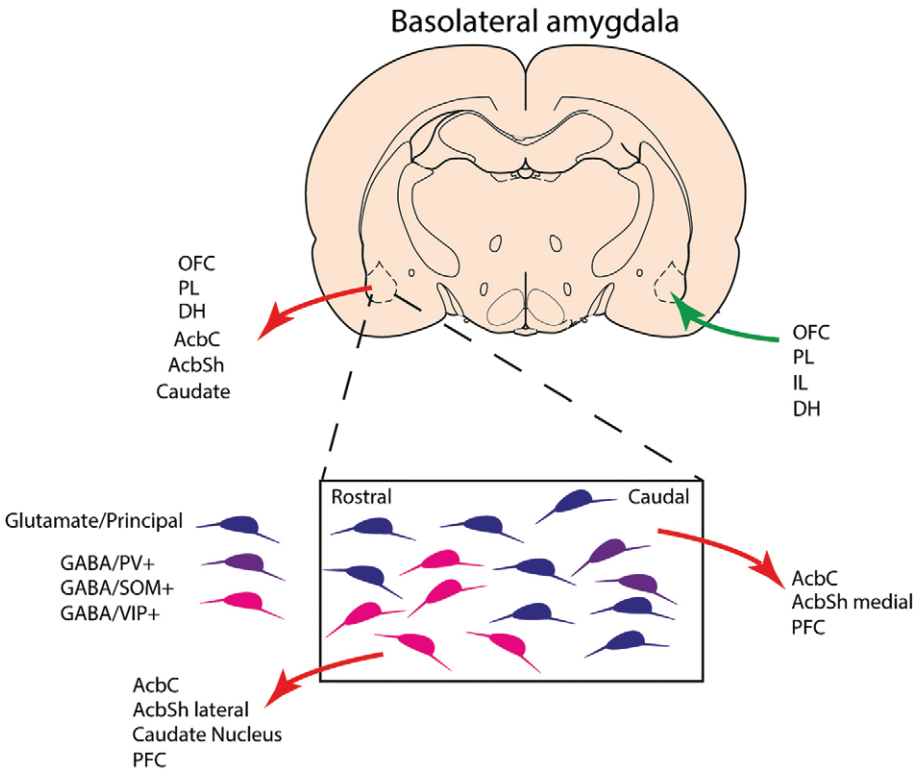

Figure 4: The BLA contributes to both extinction and context-induced reinstatement of drug seeking via its extensive connectivity with PFC, dorsal and ventral striatum. Within BLA, there is evidence for rostral-caudal differences in both connectivity and contributions to reinstatement as well extinction. Meanwhile, our understanding of the roles of specific BLA output pathways and of the cellular mechanisms for these contributions remains impoverished.

natural and drug reinforcers. This role is due, at least in part, to serial interactions with AcbSh (Millan & McNally 2011) (see below).

Nucleus accumbens shell

Similar to BLA and PFC, AcbSh (Fig. 5) shows robust activation during context-induced reinstatement of alcohol (Hamlin *et al.* 2007), sucrose (Hamlin *et al.* 2006) or cocaine (Cruz *et al.* 2014; Hamlin *et al.* 2008) seeking. This recruitment depends on D1 dopamine receptors (Hamlin *et al.* 2007) and the population of AcbSh neurons activated by exposure to the drug-taking context is causal to reinstatement (Cruz *et al.* 2014). Moreover, this recruitment is shared with context-induced reinstatement to alcohol seeking after punishment-imposed abstinence (Marchant *et al.* 2014). Reversible inactivation of AcbSh via infusions of GABA agonists attenuates context-induced reinstatement of cocaine (Fuchs *et al.* 2008) but not alcohol seeking (Chaudhri *et al.* 2008).The role for AcbSh in context-induced reinstatement of heroin-, cocaine- or alcohol-seeking reinstatement depends on complex interactions between a variety of neurotransmitters and neuropeptides including glutamate acting at $mGluR_{2/3}$ (Bossert *et al.* 2006a,2006b) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Xie *et al.* 2011), dopamine acting at D1 dopamine receptors (Bossert *et al.* 2007; Chaudhri *et al.* 2009), endogenous opioids acting at the mu-opioid receptor (MOR) (Perry & McNally 2013b) as well as the actions of cocaine- and amphetamine-regulated transcript (Millan & McNally 2012), among others.

A separate set of findings implicate AcbSh in expression of extinction of drug seeking. Among the earliest demonstrations was the finding that extinction of cocaine seeking upregulates AMPA receptor subunit ($GluR_1$ and $GluR_{2/3}$) expressions in AcbSh, but not in AcbC, and that viral-mediated overexpression of these subunits in AcbSh mimicked the effects of extinction training (Sutton *et al.* 2003). Moreover, Self *et al.* (2004) showed that extinction training normalized a variety of AcbSh responses after withdrawal from cocaine. Other studies have since confirmed this role. For example, reversible inactivation of AcbSh prevents the expression of extinction of cocaine (Fuchs *et al.* 2008; Peters *et al.* 2008) and alcohol (Chaudhri *et al.* 2008; Millan *et al.* 2010) seeking. This role for AcbSh in expression of extinction depends on glutamate actions at AMPA receptors (Millan & McNally 2011).

Much remains to be learned about AcbSh contributions to context-induced reinstatement and extinction of drug seeking. The role of different cell types within AcbSh is unknown. Systemic administration of D1 or D2 receptor antagonists prevents context-induced reinstatement of cocaine seeking (Crombag *et al.* 2002) and systemic administrations of a D1 receptor antagonist prevents this reinstatement of alcohol seeking (Hamlin *et al.* 2007). Microinjection studies show that D1 dopamine receptors in the AcbSh are the critical subtypes for context-induced reinstatement of heroin and alcohol seeking (Bossert *et al.* 2007; Chaudhri *et al.* 2009), but the roles of different medium spiny neuron (MSN)

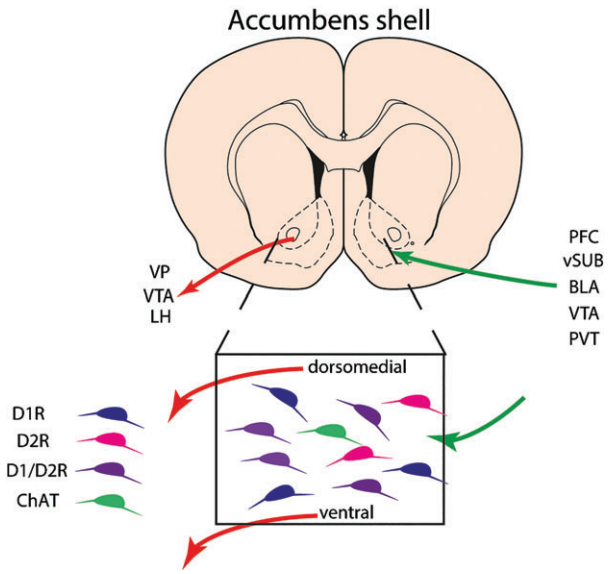

Figure 5: The accumbens shell has well-documented contributions to extinction and context-induced reinstatement of drug seeking. These are linked to various inputs from PFC, amygdala and hippocampus. The interactions between these inputs in AcbSh during extinction and reinstatement are unknown. There is evidence for dissociable roles of AcbShDm and AcbShV in extinction and reinstatement, but how these relate to differences in connectivity or to different AcbSh cell types is poorly understood.

populations in context-induced reinstatement remain to be determined and the specific cell type contributing to expression of extinction is unknown. As in the rest of striatum, the vast majority of AcbSh neurons are GABAergic MSNs differentiated by expression of the D1 or D2 receptor (Meredith *et al.* 1993). One possibility is that these two different populations contribute to the dual role of AcbSh in context-induced reinstatement vs. extinction. However, studies examining activity marker expression show that both populations of MSNs are recruited during context-induced reinstatement of methamphetamine or cocaine seeking (Cruz *et al.* 2014; Rubio *et al.* 2015). Moreover, the distinction between D1 and D2 receptor expressing MSNs, useful in broadly characterizing dorsal striatal function (Kravitz *et al.* 2012), is less recognized for the ventral striatum. Different levels of MSNs expressing both D1 and D2 receptors (Matamales *et al.* 2009), differences in MSN morphology (Meredith *et al.* 2008), anatomy (Smith *et al.* 2013) and physiology (Kupchik *et al.* 2015; Smith *et al.* 2013) have all been interpreted to mean that the D1/D2 receptor dichotomy is less clear-cut for ventral striatum.

Of particular interest is understanding the specific AcbSh afferents and efferents important for context-induced reinstatement and extinction. Here, we discuss AcbSh afferents and we consider AcbSh efferents individually in later sections. AcbSh receives glutamatergic inputs from PFC, vSUB, thalamus and BLA, among others. The existing evidence implicates each of these inputs in either context-induced reinstatement or extinction, or both. As noted above, vSUB inputs to AcbSh are important for context-induced reinstatement. The vSUB neurons projecting to the AcbSh are recruited during context-induced reinstatement of heroin seeking (Bossert *et al.* 2016) and alcohol seeking (Marchant *et al.* 2016). Pharmacological disconnection of the vSUB→AcbSh pathway prevents this reinstatement of heroin seeking (Bossert *et al.* 2016) and chemogenetic disconnection of this pathway prevents this reinstatement after punishment-imposed abstinence from alcohol seeking (Marchant *et al.* 2016). One attractive possibility is that glutamate derived from these vSUB inputs acts in combination with dopamine inputs from VTA to enable context-induced reinstatement (Crombag *et al.* 2008; Marchant *et al.* 2016). Indeed, given the findings of Luo *et al.* (2011) that a DH→LS→VTA pathway contributes to context-induced reinstatement to cocaine seeking, it will be of significant interest to determine whether the function of this vSUB→AcbSh pathway in context-induced reinstatement is because of its control over activity of VTA dopamine neurons (Floresco *et al.* 2001) (see below).

The functions of corticostriatal pathways in context-induced reinstatement and extinction remain enigmatic. The stop/go or reinstatement/extinction account of corticostriatal pathways predicts that dmPFC projections to AcbC should mediate context-induced reinstatement, whereas vmPFC projections to AcbSh should mediate expression of extinction. As is known, there is compelling evidence that the AcbSh contributes to both context-induced reinstatement and extinction, so this distinction, similar to that for the mPFC, may not accurately capture the complexity of ventral striatal contributions to reinstatement. Regardless, there is evidence from studies of reinstatement of cocaine seeking that a dmPFC→AcbC pathway is important for reinstatement because optogenetic silencing of dmPFC terminals in AcbC prevents cue as well as cocaine priming-induced reinstatement of cocaine seeking (Stefanik 2014; Stefanik *et al.* 2012). However, the role of this projection in context-induced reinstatement of seeking cocaine or other drugs remains to be determined. Further consistent with this model, Peters *et al.* (2008) reported that pharmacological disconnection of the vmPFC→AcbSh pathway prevented expression of extinction of cocaine seeking. However, Bossert *et al.* (2011, 2012) reported that a vmPFC→AcbSh pathway was recruited during context-induced reinstatement of heroin seeking and that reversible inactivation of vmPFC, selective lesioning of vmPFC-activated corticostriatal neurons or pharmacological disconnection of the vmPFC→AcbSh pathway reduced this context-induced reinstatement. It is possible that these differences in corticostriatal pathway involvement relate to differences in the mechanisms for opiates vs. psychostimulants, consistent with other important behavioral and neurobiological differences between these drug classes (Badiani *et al.* 2011). Regardless, it is reminiscent of the inconsistent effects of PFC manipulations on expression of context-induced reinstatement vs. extinction.

Other AcbSh inputs have also been directly or indirectly implicated in context-induced reinstatement or extinction. Paraventricular thalamus (PVT) provides extensive glutamatergic inputs to AcbSh (Berendse *et al.* 1992; Christie *et al.* 1987; Groenewegen & Berendse 1994; Parsons *et al.*

2007) and these interact anatomically and functionally with dopamine terminals (Parsons *et al.* 2007). Dayas and co-workers established a role for PVT in various aspects of alcohol and cocaine self-administration and cue-induced reinstatement (Dayas *et al.* 2007, 2008; James & Dayas 2013; James *et al.* 2010) that others have confirmed for cue-induced reinstatement of cocaine seeking (Matzeu *et al.* 2015). We have shown that PVT contributes to context-induced reinstatement of alcohol seeking (Hamlin *et al.* 2009) and that the PVT→AcbSh pathway is strongly recruited during this reinstatement (Hamlin *et al.* 2009). Nonetheless, a causal role for this pathway in context-induced reinstatement, and the specific AcbSh neuronal population targeted by PVT terminals during this reinstatement, remain to be established. A variety of related findings highlight the need to understand this pathway better. Goal tracking behavior in rats during appetitive conditioning depends, at least in part, on the PVT (Haight & Flagel 2014; Haight *et al.* 2015) and rats that express high levels of goal tracking show significantly greater context-induced reinstatement of cocaine seeking compared with rats expressing high levels of sign tracking (Saunders *et al.* 2014). In addition, cocaine self-administration induces complex changes and plasticity in the PVT→AcbSh projection (Neumann *et al.* 2016) and PVT synapses onto D2 receptor expressing AcbSh MSNs contribute to the motivational impact of opiate withdrawal (Zhu *et al.* 2016).

Inputs to AcbSh from cBLA are important for expression of extinction of drug seeking and preventing relapse. For example, the cBLA→AcbSh pathway is recruited during expression of extinction of alcohol seeking (Hamlin *et al.* 2009) and pharmacological disconnection of the cBLA→AcbSh pathway prevents the expression of extinction to cause reinstatement of alcohol seeking (Millan & McNally 2011). Interestingly, this cBLA→AcbSh pathway may exert a more general role in regulating the impact of drug-associated stimuli on alcohol seeking (Millan *et al.* 2015).

An important feature to consider when evaluating these findings is segregation and compartmentalization in AcbSh signaling. There is a complex relationship between cortical, amygdala and thalamic inputs to AcbSh (Wright & Groenewegen 1995). Corticostriatal and amygdalostriatal terminals overlap in AcbSh, particularly in calbindin-negative regions, and these inputs are segregated from PVT inputs in AcbSh which target calbindin-positive regions. In addition, there are circuit-level differences between the dorsal (AcbShDm) and ventral (AcbShV) regions of the medial AcbSh. For example, Zahm *et al.* (2012) locate AcbShDm as a transitional region between AcbSh and LS, showing considerable interconnectivity between these regions as well as overlap in efferents. Likewise, Thompson and Swanson (2010) show important differences in connectivity between these regions but locate AcbShDm in a circuit involving vmPFC, AcbShDm, substantia innominata, lateral hypothalamus (LH) and PVT. Consistent with this anatomical segregation, there is functional segregation of dorsal from ventromedial AcbSh in promoting and preventing relapse to drug seeking. For example, the dual role for AcbSh in expression of context-induced reinstatement vs. expression of extinction can be linked, in part, to segregated channels in AcbShV) vs. AcbShDm targeting LH (Marchant *et al.* 2009) and recent studies using deep brain stimulation have confirmed this opposing role using conditioned place preference (Martínez-Rivera *et al.* 2016). These findings are supported by other reports of functional differences between AcbShV and AcbShDm in motivation and reward (Al-Hasani *et al.* 2015; Peciña & Berridge 2005).

Nucleus accumbens core

The AcbC has a well-documented role in cue, stress and priming reinstatement of seeking a variety of drugs including cocaine, heroin and alcohol (Bossert *et al.* 2013; Kalivas & Volkow 2005; Marchant *et al.* 2013). However, its role in context-induced reinstatement remains unclear. Studies of neural activation have detected no significant increase in AcbC Fos expression during context-induced reinstatement of alcohol (Hamlin *et al.* 2007) or cocaine (Hamlin *et al.* 2008) seeking when AcbC is treated as a whole. Bossert *et al.* (2006a, 2007) originally reported that neither AcbC D1 dopamine receptor antagonism nor $mGluR_{2/3}$ agonism affected context-induced reinstatement of heroin seeking but D1 antagonism of the AcbC did reduce cue-induced reinstatement of heroin seeking. In contrast, Fuchs *et al.* (2008) showed that reversible inactivation of the AcbC via GABA agonist infusions reduced context-induced reinstatement of cocaine seeking. Likewise, Chaudhri *et al.* (2009) reported that D1 receptor antagonism of AcbC reduced context-induced reinstatement of ethanol seeking. These contrasting findings are not simply because of differences in the drug reinforcer used because Cruz *et al.* (2014) could find no evidence for a role of AcbC in context-induced reinstatement of cocaine seeking using the Daun02 inactivation method.The reasons for these discrepancies are unclear. It is possible that at least some of the positive evidences for AcbC involvement is because of the manipulation affecting AcbSh, but this explanation would struggle when pitted against these experiments as a whole. Studies of the circuitry underpinning AcbC involvement in context-induced reinstatement have been no more helpful. As noted above, a dmPFC→AcbC pathway is important for cue as well as cocaine priming-induced reinstatement of cocaine seeking (Stefanik 2014; Stefanik *et al.* 2012) but the roles of this pathway in context-induced reinstatement are unknown. Likewise, VP is a well-documented target for AcbC projections during several forms of reinstatement of drug seeking (see below), but it does not contribute to context-induced reinstatement of alcohol seeking (Perry & McNally 2013a) (see below).

Ventral pallidum

The VP (Fig. 6) serves important roles in reward and motivation (Richard *et al.* 2016; Root *et al.* 2015; Smith *et al.* 2009a). Kalivas and co-workers established VP as a critical node in the neural circuitry for reinstatement of cocaine seeking (McFarland & Kalivas 2001; McFarland *et al.* 2004; Tang *et al.* 2005; Torregrossa & Kalivas 2008), a role that has been extended to include reinstatement of heroin (Rogers *et al.* 2008) and

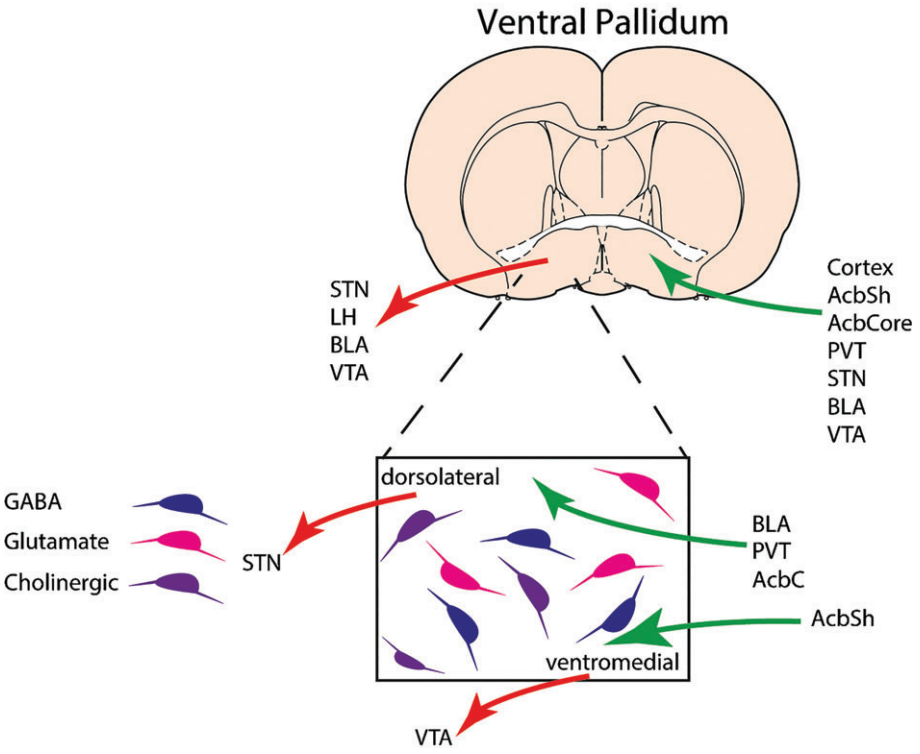

Figure 6: The VP is well established in many forms of reinstatement of drug seeking but its role in context-induced reinstatement is less well understood. Numerous VP inputs are recruited during context-induced reinstatement but there have been few causal manipulations of major VP input and output pathways during this reinstatement. Likewise, the roles of VP subregions, and the specific cell types and circuits in which they are located, require investigation.

alcohol (Perry & McNally 2013a) seeking. For example, microinjections of MOR antagonists (Perry & McNally 2013a; Tang *et al.* 2005), pharmacological inactivation (McFarland & Kalivas 2001; McFarland *et al.* 2004) or chemogenetic silencing (Mahler *et al.* 2014b) of VP prevent drug priming, cue-induced or cue + prime reinstatement of cocaine seeking in rats. This role for VP extends to context-induced reinstatement of alcohol seeking because context-induced as well as primed reinstatement of alcohol seeking are both prevented by VP microinjections of MOR antagonists (Perry & McNally 2013a).

Despite being a common locus for different forms of reinstatement, fundamental aspects of these VP contributions remain unknown. At the cellular level, VP consists of heterogeneous populations of GABAergic, glutamatergic and cholinergic releasing neurons. These neurons also express various peptides and neurotransmitters including calretinin, enkephalin, dynorphin calbindin, parvalbumin, neuropeptide Y or somatostatin (Root *et al.* 2015). Adding further complexity, some of these populations are dynamically regulated by exposure to drugs of abuse, whereas others are not. The roles of these specific population(s) of VP neurons in context-induced reinstatement and other forms of reinstatement are unclear.

The VP afferents and efferents critical for context-induced reinstatement, and indeed for other forms of reinstatement, are poorly understood. The VP receives projections from numerous regions, including cortex, Acb, PVT, subthalamic nucleus (STN), VTA and BLA, and these projections differentially target the ventromedial (VPvm) and dorsolateral (VPdl) regions of VP. A variety of lines of evidence implicate projections from AcbC to VP, which preferentially target VPdl, in cue-induced reinstatement, priming-induced reinstatement and also reacquisition of drug seeking. For example, pharmacological disconnection (McFarland & Kalivas 2001) or optogenetic silencing (Khoo *et al.* 2015; Stefanik *et al.* 2013) of the AcbC→VP pathway prevents such reinstatement for cocaine or alcohol seeking. Indeed, pallidal projections from AcbC are more important than nigral projections for this reinstatement (Stefanik *et al.* 2013). The AcbC projection uses both GABA and neurotensin (Torregrossa & Kalivas 2008) and it is tightly regulated by endogenous opioids acting at the MOR (Napier & Mitrovic 1999). This evidence for a role of VP in multiple forms of reinstatement, and the roles for striatopallidal projections in other aspects of instrumental behavior (Leung & Balleine 2013), are consistent with the widely held view that cortical–striatal–pallidal connectivity is a final common pathway for reinstatement of drug seeking (Kalivas & Volkow 2005, 2011). However, this AcbC projection is not obligatory for context-induced reinstatement. Optogenetic silencing of the AcbC→VP pathway does not reduce context-induced reinstatement of alcohol seeking (Khoo *et al.* 2015), but does prevent the reacquisition of alcohol seeking after extinction.

We have mapped activated inputs to VP during context-induced reinstatement of alcohol seeking and found recruitment of not just an AcbC→VP pathway, but also of rostral BLA→VP and PVT→VP pathways (Perry & McNally 2013a). As noted above, both BLA (Fuchs *et al.* 2007; Hamlin *et al.* 2006, 2007, 2008) and PVT (Hamlin *et al.* 2009) are necessary for context-induced reinstatement but the causal roles of their projections to VP remain to be determined in

this or other forms of reinstatement. Interestingly, AcbSh projections to VP were not recruited in this tracing study. The reason(s) for these differences in VP afferents during context-induced reinstatement is unknown. Regardless, this convergence of activated striatal, thalamic and amygdala inputs in VP during context-induced reinstatement, the sensitivity of these inputs to opioid receptor manipulations (Napier & Mitrovic 1999), combined with recent findings on the timing of reward cue-associated VP neuron activity (Richard *et al.* 2016), suggests that the role for VP in context-induced reinstatement is likely to be more complex than simply relaying ventral striatal-generated signals.

The VP efferents important for context-induced reinstatement remain poorly understood. Mahler *et al.* (2014b) identified a role for the VP→VTA projection in cue-induced reinstatement of cocaine seeking in rats. The authors distinguished between rostral and caudal VP, which differs somewhat from the classic VPdl and VPvm distinction, showing that rostral VP neurons projecting to VTA were recruited during cue-induced reinstatement of cocaine seeking and chemogenetic silencing of VP terminals in VTA or disconnection of rostral VP from VTA dopamine neurons prevented this reinstatement. Disconnections of either rostral or caudal VP from VTA had no effect on cocaine priming-induced reinstatement (Mahler *et al.* 2014b). Whether the VP→VTA pathway contributes to context-induced reinstatement is unknown. Also, unknown is whether this role is unique to the VP→VTA pathway. Given the diversity of afferents to VP recruited during reinstatement, it would not be surprising if multiple VP efferents were likewise important. For example, VPvm projects not only to VTA but also to LH (Groenewegen *et al.* 1993; Tripathi *et al.* 2012; Zahm 1989; Zahm *et al.* 1996), a region strongly implicated in context-induced reinstatement of drug seeking (see below) (Marchant *et al.* 2009, 2011, 2014), whereas VPdl projects extensively to STN and substantia nigra (SN) (Groenewegen *et al.* 1993; Tripathi *et al.* 2012; Zahm 1989; Zahm *et al.* 1996). The VP projections to STN are of considerable interest because STN manipulations reduce motivation for cocaine as well as alcohol (Baunez *et al.* 2005; Lardeux & Baunez 2007; Rouaud *et al.* 2010) and reduce reinstatement of methamphetamine seeking (Baracz *et al.* 2015). Recent unpublished work from our laboratory has shown that context-induced reinstatement of alcohol seeking is associated with recruitment of both VP→VTA and VP→STN projections and it can be prevented by chemogenetic disconnection of either pathway (A. A. Prasad, unpublished observations). An attractive possibility is that segregated transpallidal channels, such as AcbSh→VPvm→LH/VTA and AcbC→VPdl→STN/SN (Groenewegen *et al.* 1993; Zahm & Heimer 1990), interface with distinct corticostriatal and amygdalostriatal circuits to mediate distinct aspects of reinstatement and extinction.

Hypothalamus

The tuberal hypothalamus, comprising dorsomedial, perifornical and LH, plays important roles in expression of context-induced reinstatement and expression of extinction of drug seeking (Fig. 7).

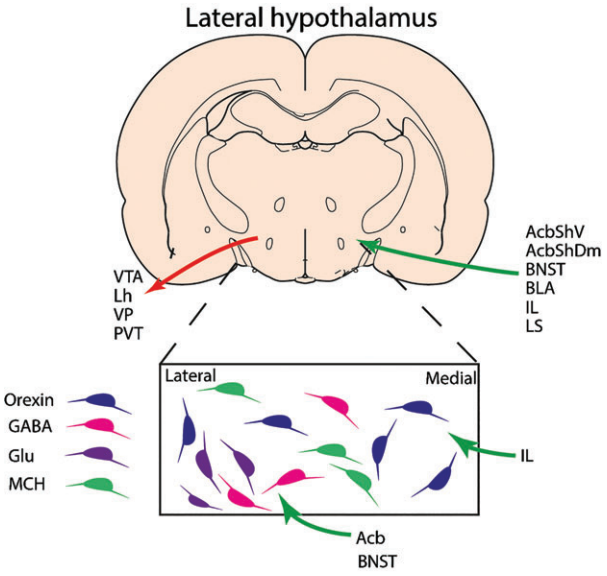

Figure 7: The LH and MDH serve opposing roles in promoting context-induced reinstatement and extinction of drug seeking, respectively. These opposing roles have been linked to different inputs but how these relate to the various cell types in LH, and their major outputs, is unknown.

The LH has a key role in context-induced reinstatement. This has been shown via recruitment of hypothalamic neurons during context-induced reinstatement of seeking sucrose (Hamlin *et al.* 2006), alcohol (Hamlin *et al.* 2007) and cocaine (Hamlin *et al.* 2008). It has also been shown by demonstrations that reversible inactivation of LH via GABA agonist infusions reduces context-induced reinstatement of alcohol seeking (Marchant *et al.* 2009). This role for LH does not depend on how abstinence from drug seeking is imposed because it is shared with context-induced reinstatement of alcohol seeking following punishment (Marchant *et al.* 2014). Moreover, LH contributes to reinstatement in both instrumental drug seeking and conditioned place preference procedures, across a variety of drugs including morphine (Harris *et al.* 2005), cocaine (Kallupi *et al.* 2012; Sartor & Aston-Jones 2012), amphetamine (Schmeichel & Berridge 2013) and nicotine (Plaza-Zabala *et al.* 2013).

Much like the other brain regions discussed here, the critical LH cell types as well as their afferents and efferents during context-induced reinstatement remain unclear. Significant effort has been directed toward understanding the role of orexin neurons in reinstatement of drug seeking (Fig. 8). This was stimulated by the initial demonstration that lateral hypothalamic orexin neurons are recruited during reinstatement of an opiate-conditioned place preference and that activation of LH orexin neurons is sufficient to reinstate this place preference (Harris *et al.* 2005). This was closely followed by reports that the OX_1 receptor antagonist SB-334867 reduces stress-induced reinstatement of cocaine seeking (Boutrel *et al.* 2005) and cue-induced reinstatement of alcohol seeking (Lawrence *et al.* 2006). Studies on the

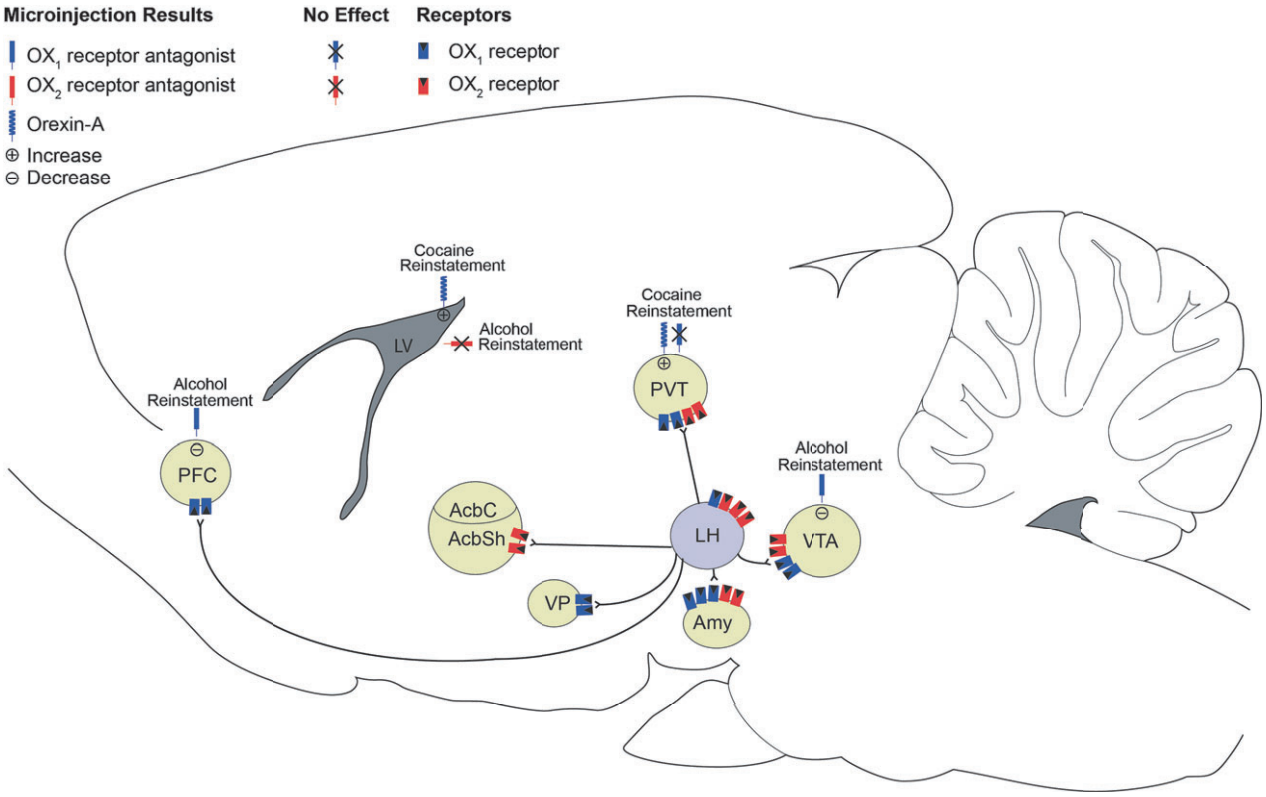

Figure 8: Orexin neurons originate in the hypothalamus and project widely throughout the brain. The two receptor subtypes, OX_1 and OX_2, are present throughout key reward regions at differing levels. Microinjections of orexin-A have been shown to promote reinstatement of cocaine seeking when targeting either the lateral ventricle or the PVT, but OX_1 antagonism in the PVT has no effect. Antagonist studies on alcohol seeking have also had mixed results, with reductions in reinstatement owing to OX_1 antagonism in the VTA or PFC, but not following central OX_2 antagonism.

role of orexin neurons in context-induced reinstatement have yielded inconsistent results. Using colocalization of c-Fos and the orexin protein, we reported that orexin neurons in the LH were recruited during context-induced reinstatement of cocaine (Hamlin *et al.* 2008) but not alcohol (Hamlin *et al.* 2007) or sucrose (Hamlin *et al.* 2006) seeking. A similar lack of recruitment during context-induced reinstatement of alcohol seeking following punishment was reported by Marchant *et al.* (2014). In contrast, lateral orexin neurons were recruited during context-induced reinstatement of alcohol seeking in another study (Moorman *et al.* 2016). An important reason for the difference between these results is the nature of the control group. When controls matched on behavioral and pharmacological training histories as well as exposure to stimuli on test are included, then there is little evidence for a selective recruitment of orexin neurons during context-induced reinstatement of alcohol seeking but there is evidence for this reinstatement of cocaine seeking. Regardless, across each of these studies, there were also differences in recruitment of the medial and lateral orexin fields, with the medial fields consistently recruited by handling, transport and being tested, regardless of the training history of the context and whether there was reinstatement, consistent with a role for the medial orexin field in arousal (Harris & Aston-Jones 2006). The impacts of direct manipulation of the orexin system generally agree with these findings. Consistent with the robust recruitment of lateral orexin neurons during context-induced reinstatement of cocaine seeking, this reinstatement is prevented by pretreatment with SB-334867 (0–30 mg/kg) (Smith *et al.* 2010), whereas selective knockdown of orexin protein expression does not prevent context-induced reinstatement of alcohol seeking (Prasad & McNally 2014).

The reasons for these discrepancies between orexin contributions to context-induced reinstatement of cocaine vs. other drugs remain unclear. Indeed, this variability of the effects of orexin manipulations on context-induced reinstatement is reflective of the broader variability of orexin manipulations on appetitive behavior. One explanation is that orexin's role in promoting appetitive behavior is as a motivational activator, with the orexin system important for promoting drug seeking and other appetitive behaviors under conditions of high effort (Mahler *et al.* 2014a). This is supported by findings that systemic SB-334867 reduces progressive ratio breakpoint, cue-induced reinstatement, context-induced renewal and where the unit-price of cocaine is high but not when it is low (Brodnik *et al.* 2015; España *et al.* 2010; Smith *et al.*

2009a, 2009b, 2010). SB-334867 can also reduce operant self-administration of cocaine when the fixed ratio (FR) is 5 responses per infusion (Hollander *et al.* 2008), but not under FR1 conditions (España *et al.* 2010; Smith *et al.* 2009b). A similar idea suggested by Shoblock *et al.* (2010) explains the lack of effect of the OX_1 antagonist SB-408124, on operant responding for alcohol. The largest effects of orexin receptor antagonists are typically observed in animals with increased willingness to work for and consume drug rewards, such as in animals having a high alcohol preference (Moorman & Aston-Jones 2009), in animals selectively bred for high levels of alcohol preference (Lawrence *et al.* 2006) or in animals with extended (25–40 days) access to alcohol (Brown *et al.* 2013; Richards *et al.* 2008).

Nonetheless, a motivational activator account does not explain the variability in effects of orexin manipulations across reinstatement and other drug-seeking studies. While orexin antagonism does not block FR1 responding for cocaine, it does block FR1 responding for heroin (Smith & Aston-Jones 2012). Similarly, OX_2 antagonism blocks FR1 responding for heroin in long (12 h) but not short access (1 h) sessions (Schmeichel *et al.* 2015). Moreover, orexin receptor antagonism has no effect on sucrose self-administration under an FR3 schedule and a low (∼1%) sucrose concentration (Brown *et al.* 2013), and has no effect on reinstatement for similarly dilute sucrose solutions (Brown *et al.* 2015). An FR3 schedule for a low sucrose concentration represents a high unit cost, precisely the conditions under which the motivational activator theory would predict that the orexin system should be involved. Moreover, the degree to which the orexin system acts as a motivational activator may vary between reinforcers despite similar levels of operant responding. For example, Nair *et al.* (2008) reported that SB-334867 could prevent high-fat pellet self-administration but not reinstatement induced by orexin-A, pellet priming or yohimbine. Borgland *et al.* (2009) reported that regular food and high-fat chocolate pellets had a similar breakpoint following administration of a vehicle solution, but that the breakpoint for high-fat chocolate pellets was selectively attenuated by SB-334867. The breakpoint for cocaine was also reduced by SB-334867 but from an even lower baseline than for either regular food or high-fat chocolate pellets. For cocaine, a high unit cost or FR schedule is required (Brodnik *et al.* 2015; Hollander *et al.* 2012; Smith *et al.* 2009b), whereas for heroin the FR schedule is less important than the length of access (Schmeichel *et al.* 2015).

Assessing drug-induced plasticity in orexin neurons (Yeoh *et al.* 2012) as well as the roles of other LH cell types and their circuit-level drivers during reinstatement will be important to resolving these issues and to providing a coherent account of hypothalamic contributions to reinstatement of drug seeking (Prasad & McNally 2014). Optogenetic and chemogenetic studies show that non-orexin lateral hypothalamic glutamatergic and GABAergic populations exert profound control over feeding and appetitive motivation independent of orexin neurons (Jennings *et al.* 2015; Nieh *et al.* 2015). Both Acb (O'Connor *et al.* 2015) and bed nucleus of the stria terminalis (BNST) (Jennings *et al.* 2013) inputs target these glutamatergic and GABAergic neurons, and not orexin neurons, to regulate appetitive motivation. These non-orexin LH neurons, and their inputs, are important targets for future studies on the mechanisms for reinstatement of drug seeking.

There has been progress in identifying afferents to LH during reinstatement. The AcbSh is an important source of inputs to LH during context-induced reinstatement of alcohol seeking (Marchant *et al.* 2009, 2014), with evidence that neurons located in AcbShV are especially important for reinstatement whereas those in AcbShDm are important for expression of extinction (see above). This recruitment of an AcbShV→LH pathway during reinstatement is independent of how abstinence from alcohol seeking is imposed, but the causal role of the AcbShV→LH pathway in reinstatement remains to be determined. Larson *et al.* (2015) recently reported that a single session of optogenetic stimulation of an AcbSh→LH pathway had no initial effect on self-administration of cocaine under a progressive ratio schedule but did have a delayed facilitatory effect on a progressive ratio schedule. This suggests complexity in AcbSh–LH interactions. Our own unpublished studies show that the effects of optogenetic stimulation in the AcbSh→LH pathway on alcohol seeking are gated by the presence vs. absence of extinction training (G. Gibson, unpublished observations). The LH targets of these AcbSh inputs are also poorly understood. The Acb inputs to LH have been reported to terminate in a region significantly rostral to the orexin field (Sano & Yokoi 2007), that contains predominantly glutamatergic and GABAergic neurons. A role for D1 receptor expressing AcbSh inputs onto LH GABAergic neurons in regulating feeding and appetitive motivation has been established (O'Connor *et al.* 2015). This potential segregation of AcbSh inputs from the orexin field could explain the lack of consistent effects of orexin manipulations on context-induced reinstatement.

Septal inputs to LH are also likely relevant for context-induced reinstatement. There is a complex relationship between LS, AcbSh and hypothalamus because of the significant interconnectivity between AcbSh, notably its rostral dorsomedial region, and the LS (Zahm *et al.* 2012), as well as the sharing of similar projections to the lateral preoptic area/LH continuum (Zahm *et al.* 2012) (see above). Pharmacological disconnection implicates an LS→LH pathway in the expression of Pavlovian cocaine-conditioned place preference (Sartor & Aston-Jones 2012) and an LS→VTA pathway in context-induced reinstatement of cocaine seeking (Luo *et al.* 2011), suggesting that for context-induced reinstatement of instrumental responding, LS projections to LH may not be important. However, the distinction between LS→VTA and LS→LH pathways and whether these are separate or collaterals of common LS neurons remain to be determined. Finally, the roles of other inputs to LH, especially from BNST (Jennings *et al.* 2013) and BLA (Petrovich *et al.* 2005) in reinstatement of drug seeking remain to be determined.

The LH outputs for context-induced reinstatement remain poorly understood. The VTA is an obvious target. The LH provides extensive inputs to VTA (Watabe-Uchida *et al.* 2012) and these projections are recruited during cue-induced reinstatement of cocaine seeking (Mahler & Aston-Jones 2012). These inputs are derived from numerous LH cell classes, including orexin (Borgland *et al.* 2006), GABA (Nieh *et al.*

2015) and glutamate (Nieh *et al.* 2015) neurons, that have direct and indirect effects on VTA dopamine neuron activity as well as pronounced effects on appetitive motivation and behavior (Barbano *et al.* 2016; Nieh *et al.* 2015, 2016). However, LH targets relevant for appetitive motivation extend beyond VTA to include lateral habenula (Stamatakis *et al.* 2016) and VP, among other regions. Mapping the roles of these outputs in reinstatement of drug seeking, determining whether outputs are shared across different forms of reinstatement and/or different drug classes, will be important to determine.

Additional complexities in understanding hypothalamic contributions to expression of context-induced reinstatement and extinction of drug seeking come from studies of the perifornical and dorsomedial hypothalamus. We reported that the expression of extinction of alcohol seeking was associated with significant recruitment of IL inputs (Thompson & Swanson 1998) to both the dorsomedial and perifornical hypothalamus (Marchant *et al.* 2010) and that pharmacological silencing of these regions selectively prevented the expression of extinction. Given that we did not observe any differences in either IL inputs or silencing between the perifornical and dorsomedial regions, we referred to these as the mediodorsal part of the tuberal hypothalamus (MDH) (Marchant *et al.* 2010). This role for the MDH in promoting extinction expression is in functional opposition to the role of LH in promoting context-induced reinstatement, and is reminiscent of the functional opposition between these regions in feeding and appetitive motivation (Elmquist *et al.* 1998; Porrino *et al.* 1983). Interestingly, MDH contributions to expression of extinction of alcohol seeking depend on the recruitment of peptidergic neurons in the MDH, namely orexin neurons and specifically on projections of these neurons to PVT. However, it is the prodynorphin content of these neurons (Chou *et al.* 2001), not orexin, that is important for expression of extinction of alcohol seeking and prevents reinstatement because context-induced reinstatement is prevented by microinjections of kappa opioid receptor agonists into PVT. Thus, both IL→MDH and prodynorphin/orexin MDH→PVT pathways are recruited during expression of extinction. These findings highlight two important features of hypothalamic contributions to reinstatement and extinction of drug seeking. First, medial and lateral hypothalamic regions are located in anatomically and functionally distinct circuits that are recruited to promote (lateral) vs. prevent (medial) reinstatement. Second, the release of different products (orexin vs. prodynorphin-derived peptides) of the same cell class in the same circuits can have opposing influences on reinstatement and motivation (Li *et al.* 2014; Muschamp *et al.* 2014), suggesting that modes of activity within these circuits influencing which peptide is released may be important in determining reinstatement vs. extinction of drug seeking.

Ventral tegmental area and substantia nigra

The VTA and SN (Fig. 9) have received surprisingly little attention in context-induced reinstatement. As noted above,

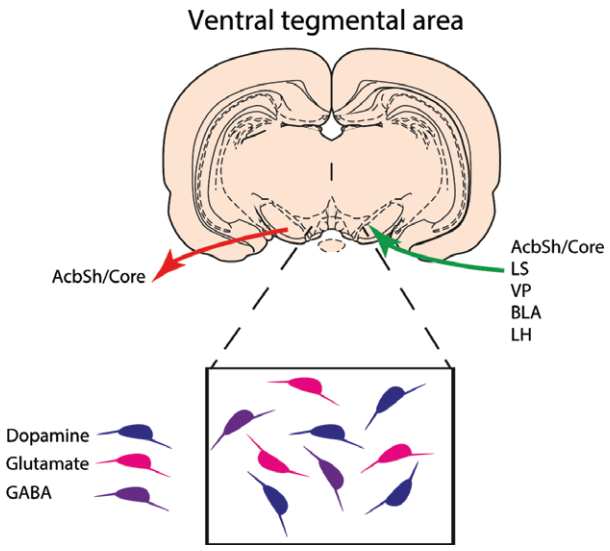

Figure 9: The contributions of VTA to context-induced reinstatement and extinction of drug seeking are surprisingly poorly understood. Inputs from LS have been implicated, but the roles of other major VTA inputs are unknown. To date, little contact has been made between our increased knowledge of VTA cell types, circuitry and the extinction and context-induced reinstatement of drug seeking.

systemic administration of dopamine D1 or D2 receptor antagonists prevents context-induced reinstatement of cocaine seeking (Crombag *et al.* 2002) and these administrations of a D1 receptor antagonist prevent context-induced reinstatement of alcohol seeking (Hamlin *et al.* 2007). Moreover, as reviewed above, microinjections of D1 dopamine receptor antagonists into the Acb, among other regions, prevent context-induced reinstatement of heroin, cocaine or alcohol seeking. However, there have been few attempts to relate context-induced reinstatement to VTA or SN function. Bossert *et al.* (2004) reported that glutamate actions in VTA were critical for context-induced reinstatement of heroin seeking because this reinstatement was attenuated by VTA microinjections of an $mGluR_{2/3}$ agonist. However, the specific roles of VTA dopamine or other neurons in this reinstatement remain to be determined.

Early attempts to map the VTA and SN afferents recruited during context-induced reinstatement of cocaine seeking were unsuccessful (Hamlin *et al.* 2008), whereas such attempts during cue-induced reinstatement of cocaine seeking showed an array of activated inputs (Mahler & Aston-Jones 2012). Luo *et al.* (2011) identified a role for an LS→VTA pathway in context-induced reinstatement of cocaine seeking using pharmacological disconnection techniques, but to date this remains the only demonstration of a specific VTA afferent pathway recruited during this reinstatement. This contrasts markedly with other forms of reinstatement. Of particular interest, Mahler *et al.* (2014b) used chemogenetic approaches to identify a role for the rostral VP→VTA pathway in cue-induced reinstatement of cocaine seeking. They showed that VTA tyrosine

hydroxylase (TH)-containing neurons were necessary for cue-induced reinstatement but not because of direct input from VP terminals, raising the possibility of complex intra-VTA circuits in determining this recruitment. The various corticostriatal, amygdalostriatal, striatopallidal and hypothalamic circuits reviewed above and recruited during context-induced reinstatement converge on VTA as well as SN to have multiple effects on GABAergic, glutamatergic and TH neurons (Dobi *et al.* 2010; Li *et al.* 2012; Qi *et al.* 2016; Xia *et al.* 2011; Zhang *et al.* 2015). Our own unpublished work suggests that several of these pathways are necessary for context-induced reinstatement of alcohol seeking because chemogenetic disruption of the VP→VTA (A. A. Prasad, unpublished observations) or optogenetic silencing of the AcbSh→VTA (G. Gibson, unpublished observations) pathway prevent this reinstatement, but both of these effects may be independent of VTA TH neurons. However, unfortunately to date, little contact has been made between the significantly increased knowledge of the organization and function of VTA input and output pathways (Beier *et al.* 2015; Bocklisch *et al.* 2013; Brown *et al.* 2012; Faget *et al.* 2016; Lammel *et al.* 2013; Nieh *et al.* 2015; Watabe-Uchida *et al.* 2012; Xia *et al.* 2011) and reinstatement or extinction or drug seeking. This is a fertile area for future research.

Further issues

The relationship between the mechanisms for context-induced reinstatement and extinction reviewed here and that for other aspects of the maladaptive nature of drug seeking is unclear. A persistent propensity to relapse is a cardinal feature of addiction across all drug classes and is modeled well by the data reviewed here. However, these models are not intended to capture other features of the addiction-like state such as loss of control over intake, compulsive drug use and drug use in the face of adverse consequences. Behavioral phenomena such as escalation of intake, transition to habit, impulsivity and resistance to punishment have been proposed to model an addiction-like state and to mark this state as different from that normally studied in shorter access drug self-administration designs. The mechanisms that underpin these phenomena frequently occur in cortical, amygdala and striatal circuits overlapping considerably with those reviewed here (Bari & Robbins 2013; Everitt & Robbins 2005; Kasanetz *et al.* 2010, 2013). This is unsurprising. The circuits essential for extinction and reinstatement are central to action selection, decision-making and inhibitory control. A key unanswered question is if, and how, the drug-induced changes that occur in these circuits, and are proposed to underpin an addiction-like state, alter the mechanisms for extinction and reinstatement reviewed here.

Relatedly, there is increasing interest in the clinical and cognitive neuroscience predictors of successful abstinence (Garavan *et al.* 2013). Emerging from studies of cognitive control, there is evidence for improvements in prefrontal cortical function, and possibly structure, as well as alterations in corticostriatal connectivity during successful abstinence from nicotine, cocaine, alcohol and heroin (Addicott *et al.* 2015; Bell *et al.* 2011; Brody & McClernon 2015; Connolly *et al.* 2012; Loughead *et al.* 2015; Nestor *et al.* 2011; Sweitzer *et al.* 2016; Wang *et al.* 2012). Again, given their fundamental roles in action selection, decision-making and working memory, the overlap between these circuits predicting successful abstinence and those circuits identified through animal studies of extinction and reinstatement is reassuring, but not surprising. What is lacking is the ability to parse these circuits experimentally or treat them therapeutically with the same precision to assess the possible clinical benefit of the knowledge reviewed here. One approach to this problem is provided by the work of Luscher *et al.* (2015). They have used *in vitro* optogenetic protocols to develop specific *in vivo* deep brain stimulation protocols that reverse both the synaptic and behavioral pathologies caused by psychostimulants (Creed *et al.* 2015; Luscher *et al.* 2015). However, much more work is needed if the translational potential of this field is to be achieved.

Conclusions

Here, we have reviewed some of the literature on how contexts can act to promote or prevent relapse to drug seeking. Clearly, much has been learned about these mechanisms at both the behavioral and neural levels. Our understanding of the key brain regions for extinction and context-induced reinstatement of drug seeking, their connectivity and neuropharmacology has advanced significantly. As reviewed here, there is overlap, at multiple levels of the neuraxis, between these mechanisms across different drug reinforcers but there are also unresolved differences. There is also overlap between the mechanisms for context-induced reinstatement and other forms of reinstatement of drug seeking despite important differences.

Nonetheless, as indicated throughout this review, much remains to be learned. Many fundamental questions about the mechanisms for context-induced reinstatement remain unanswered. Our view is that current understanding, although significant, defies explanations in terms of neural circuits and functions at the level of brain structures and their connectivity. Our current models of the brain mechanisms for reinstatement of drug seeking have served as useful heuristics, especially for translating findings across species and across disorders of motivation. However, the literature reviewed here shows that these mechanisms are more nuanced than most contemporary models allow. There is significant functional compartmentalization and segregation within these structures during reinstatement and extinction of drug seeking that parallels their anatomical segregation into circuits and channels. A key challenge is to understand how these circuits and channels are organized and how different modes of activity of ensembles of neurons within them promote abstinence or relapse to drug seeking.

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