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Role of corticostriatal circuits in context-induced reinstatement of drug seeking

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Abstract

Drug addiction is characterized by persistent relapse vulnerability during abstinence. In abstinent drug users, relapse is often precipitated by re-exposure to environmental contexts that were previously associated with drug use. This clinical scenario is modeled in preclinical studies using the context-induced reinstatement procedure, which is based on the ABA renewal procedure. In these studies, context-induced reinstatement of drug seeking is reliably observed in laboratory animals that were trained to self-administer drugs that are abused by humans.

In this review, we summarize neurobiological findings from preclinical studies that have focused on the role of corticostriatal circuits in context-induced reinstatement of heroin, cocaine, and alcohol seeking. We also discuss neurobiological similarities and differences in the corticostriatal mechanisms of context-induced reinstatement across these drugs classes. We conclude by briefly discussing future directions in the study of context-induced relapse to drug seeking in rat models.

Our main conclusion from the studies reviewed is that there are both similarities (accumbens shell, ventral hippocampus, basolateral amygdala) and differences (medial prefrontal cortex its projections to accumbens) in the neural mechanisms of context-induced reinstatement of cocaine, heroin, and alcohol seeking.

Keywords

abstinence; alcohol; cocaine; context; craving; cue; extinction; drug self-administration; heroin; punishment; reinstatement; relapse; review

1. Introduction

Drug addiction is characterized by persistent relapse vulnerability during abstinence (Hunt et al., 1971; O'Brien, 2005). This *relapse* is a defining feature of drug addiction and a major impediment to successful treatment (Sinha et al., 2011) (Box 1). In abstinent drug users,

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relapse is often precipitated by re-exposure to environmental *contexts* that are associated with drug use (O'Brien et al., 1992) (Box 1). This clinical scenario is modeled in preclinical studies using a *context-induced reinstatement* procedure (Crombag and Shaham, 2002; Crombag et al., 2008), which is based on the ABA *renewal* procedure (Bouton and Bolles, 1979; Nakajima et al., 2000) (Box 1). In this procedure, laboratory animals are initially trained to self-administer a drug in a specific environmental context (context A). Following self-administration training, drug seeking is extinguished through non-reinforcement in an alternative, distinct, environmental context (context B). The contexts typically differ in their auditory, visual, tactile, olfactory, and circadian properties. After repeated extinction sessions, drug seeking is extinguished and the laboratory animal is then tested, in extinction conditions, for context-induced reinstatement in the original training context. The operational definition of *reinstatement* in this procedure is significantly higher non-reinforced operant responding in the original training context A than in the extinction context B (Box 1). Since the initial demonstration with speedball (a heroin-cocaine combination) (Crombag and Shaham, 2002), context-induced reinstatement of extinguished drug seeking has been observed with several major drugs of abuse (Crombag et al., 2008), including heroin (Bossert et al., 2004), cocaine (Crombag et al., 2002), alcohol (Burattini et al., 2006), and nicotine (Diergaarde et al., 2008).

In line with the aims of this special edition of *Brain Research*, in this review we summarize neurobiological findings from preclinical studies that have focused on the role of cortical and corticostriatal circuits in context-induced reinstatement of drug seeking. During the last twelve years, many studies indicate a role of several corticostriatal projections in context-induced reinstatement of drug seeking (Bossert et al., 2013). Below, we discuss these neurobiological findings separately for heroin, cocaine, and alcohol (see Table 1 for summary of findings). In addition to corticostriatal pathways, we also discuss the role of ventral tegmental area (VTA) in context-induced reinstatement of drug seeking, because dopamine (Fallon and Moore, 1978) and glutamate (Yamaguchi et al., 2007; Yamaguchi et al., 2011) neurons in this brain region project to the different corticostriatal areas that are covered in our review.

Note that although there are published studies on context-induced reinstatement of nicotine or methamphetamine seeking (Diergaarde et al., 2008; Widholm et al., 2011; Wing and Shoaib, 2008), we do not include these studies in our review because these studies only assessed the effect of systemic drug injections on context-induced reinstatement. We also do not review studies on relapse to drug seeking after periods of abstinence (e.g., incubation of cocaine craving) in which a single extinction session in the presence of contextual drug cues (the self-administration chamber) and discrete drug infusion cues (tone, light) is used to assess relapse to drug seeking (Fuchs et al., 2006; Marchant et al., 2013b; Pickens et al., 2011). We exclude these studies, because we and others have shown that responding in the extinction tests used to study relapse after abstinence is context-independent (Crombag et al., 2008).

2. Role of corticostriatal inputs in context-induced reinstatement of drug seeking

a. Heroin

The first preclinical reinstatement study on heroin-priming-induced reinstatement of heroin seeking was published in 1983 (de Wit and Stewart, 1983). Since then, several labs have investigated mechanisms of reinstatement of heroin seeking induced by heroin priming, stress, and discrete cues (Bossert et al., 2013; Shaham et al., 2000; Shalev et al., 2002). It has been known for many years that environmental contexts associated with heroin and other opiate use play a critical role in relapse during abstinence (Robins et al., 1974; Wikler, 1973). Therefore, a decade ago we began a series of studies on the neurobiological substrates of context-induced reinstatement of heroin seeking. Based on Bouton's research and theoretical writing (Bouton and Swartzentruber, 1991; Bouton, 2002), and our initial study with speedball (a heroin-cocaine combination) (Crombag and Shaham, 2002), our original intention was to study mechanisms underlying the *occasion setter's* properties of the drug-associated context, or the ability of the context to 'renew' the conditioned response to the discrete cue (compound tone-light) previously paired with heroin injections after extinction of the response to these cues in a non-drug context (Box 1).

We initially assessed the effect of systemic injections of LY379268, a group II metabotropic glutamate receptor (mGluR2/3) agonist which acts centrally to decrease evoked glutamate release (Schoepp, 2001), on context-induced reinstatement of heroin seeking (Bossert et al., 2004). We used LY379268 because previous studies found that systemic injections of LY379268 or other mGluR2/3 agonists decrease several behavioral effects of drugs of abuse, including opiate withdrawal symptoms (Vandergriff and Rasmussen, 1999) and *discriminative cue-induced reinstatement* of cocaine seeking (Baptista et al., 2004) (Box 1). We found that systemic injections of LY379268 dose-dependently decreased context-induced reinstatement of heroin seeking (Bossert et al., 2004) at doses that did not affect heroin self-administration (Bossert et al., 2005) or high rates of responding for a sucrose solution (Bossert et al., 2006b). We then examined the role of mGluR2/3 in VTA, the cell body region of the mesolimbic dopamine system, because this brain area is involved in opiate reward and reinstatement (Stewart, 1984; Wise, 1989) and dopaminergic output from VTA is controlled in part by glutamate afferents from several brain areas (Sesack et al., 2003). We found that injections of LY379268 into VTA, but not substantia nigra, decrease context-induced reinstatement of heroin seeking (Bossert et al., 2004); however, this decrease was partial and not dose-dependent.

Based on this finding, we then studied the effect of LY379268 injections into nucleus accumbens, a terminal region of the mesolimbic dopamine system and an area that receives glutamatergic input from several brain regions (Brosgé et al., 1993; Groenewegen et al., 1999). We found that injections of LY379268 into medial accumbens shell decreased context-induced reinstatement of heroin seeking (Bossert et al., 2006a). Injections into accumbens core also decreased this reinstatement but only at doses 3-10 times higher than that required in the accumbens shell, suggesting that the higher effective dose in the core was due to diffusion to the shell. None of the doses tested in dorsal striatum were effective.

VTA and accumbens shell are the respective cell body and terminal regions of the mesolimbic dopamine system (Fallon and Moore, 1978). Thus, our findings suggest that the role of glutamate in context-induced reinstatement involves modulation of mesolimbic dopamine function. Indeed, early neuroanatomical studies indicate that the cell body region of the mesocorticolimbic dopamine system in the VTA plays a critical role in drug-induced reinstatement. Activation of these midbrain dopamine neurons by local morphine infusions reinstates heroin seeking (Stewart, 1984) and systemic injections of dopamine D1-like, D2-like, and mixed dopamine antagonists decrease heroin-priming induced reinstatement (Shaham and Stewart, 1996). Furthermore, McFarland and Ettenberg (1997) found that the dopamine receptor antagonist, haloperidol, reduces runway time signaled by a heroin discriminative cue after being previously paired with a heroin injection. Additionally, local application of LY379268 reduces dopamine levels in accumbens shell, but not core (Greenslade and Mitchell, 2004), a finding that is highly relevant to our results.

We found that injections of the dopamine D1-like receptor antagonist SCH 23390 either systemically, or directly into medial and lateral accumbens shell, but not core, decreases context-induced reinstatement of heroin seeking (Bossert et al., 2007). These data are consistent with findings that SCH 23390 and a more selective dopamine D1 receptor antagonist, SCH 39166, decrease context- and discriminative-cue-induced reinstatement of cocaine, alcohol, and sucrose seeking (Ciccocioppo et al., 2001; Crombag et al., 2002; Hamlin et al., 2007; Hamlin et al., 2008; Weiss et al., 2001) and that systemic SCH 23390 injections decrease context-induced increases in Fos protein expression, a marker of neural activity (Morgan and Curran, 1991), in accumbens shell (Hamlin et al., 2007; Hamlin et al., 2008). These data are also in agreement with those of Ghitza and colleagues (2003) who found that re-exposure to discriminative cues that predict cocaine availability increases neuronal activity in accumbens shell but not core.

Because injections of SCH 23390 into accumbens shell decrease context-induced reinstatement, our previous finding that LY379268 was effective in VTA is likely due to decreases in VTA dopamine transmission. This would then result in decreases in accumbens shell dopamine release and, consequently, less stimulation of local D1-family receptors. There is evidence that dopamine transmission in VTA is partly controlled by excitatory glutamate projections from several brain areas (Geisler et al., 2007) and based on electrophysiological and neuroanatomical studies (Manzoni and Williams, 1999; Rouse et al., 2000), injections of LY379268 into VTA should activate local presynaptic inhibitory mGluR2, resulting in decreased glutamate transmission, and consequently, decreased dopamine transmission.

We further characterized the role of striatal dopamine D1-like receptors and found that injections of SCH 23390 into dorsolateral, but not dorsomedial, striatum decrease context-induced reinstatement (Bossert et al., 2009). These data are consistent with those of Rogers et al. (2008) who reported that reversible inactivation of dorsolateral striatum decreases heroin priming- and *discrete cue-induced reinstatement* of heroin seeking (Box 1). We had previously found that injections of SCH 23390 into lateral accumbens shell also decrease this reinstatement. Since lateral shell neurons project directly to substantia nigra compacta (Usuda et al., 1998), which in turn project to dorsal striatum (Beckstead et al., 1979), we

used an *asymmetric disconnection procedure* (Gold, 1966) to examine whether injections of SCH 23390 into one hemisphere of dorsolateral striatum combined with injections of SCH 23390 into the contralateral hemisphere of lateral accumbens shell would disrupt this reinstatement (Box 1). This manipulation had no effect on context-induced reinstatement of heroin seeking, suggesting that D1-receptor-mediated dopamine transmission in dorsolateral striatum and lateral accumbens shell are independently involved in this reinstatement (Bossert et al., 2009).

Our next question was which glutamatergic projection/s to accumbens shell is/are involved in context-induced reinstatement of heroin seeking. Accumbens shell receives projections from medial prefrontal cortex (mPFC), thalamus, amygdala, and hippocampus (Groenewegen et al., 1999), and we found that re-exposure to the heroin context increases Fos protein expression in ventral mPFC and ventral subiculum/CA1 ((Bossert et al., 2011; Bossert et al., 2012); Bossert et al., unpublished findings). Subsequently, we found that reversible inactivation (using the GABA_A+ GABA_B receptor agonist mixture muscimol +baclofen) of ventral (comprised of ventral prelimbic and infralimbic cortex), but not dorsal (comprised of dorsal prelimbic/anterior cingulate), mPFC decreases context-induced reinstatement of heroin seeking (Bossert et al., 2011). This effect was mimicked by selectively inactivating ventral mPFC Fos-activated neurons using the novel *Dam02 inactivation method* (Koya et al., 2009) (Box 1). We then asked whether the projections from ventral mPFC to accumbens shell play a role in context-induced reinstatement and found that this reinstatement was associated with increased Fos expression in ventral mPFC neurons that project to accumbens shell, as assessed by double-labeling of Fos with Fluorogold, a retrograde tracer (Bossert et al., 2012). Furthermore, we confirmed the functional role of this projection in context-induced reinstatement by demonstrating that reversible inactivation of ventral mPFC in one hemisphere combined with dopamine D1 receptor blockade into contralateral or ipsilateral accumbens shell decreases this reinstatement (Bossert et al., 2012). More recently, we also established a functional role for ventral hippocampus in context-induced reinstatement. We found that reversible inactivation of ventral subiculum/CA1, but not dorsal subiculum/CA1, decreases this reinstatement (Bossert and Stern, 2014). These data are also consistent with our previous neurocircuitry findings, because ventral subiculum/CA1 projects mainly to caudomedial accumbens whereas dorsal subiculum/CA1 projects mainly to rostromedial accumbens (Groenewegen et al., 1987).

Taken together, we identified a role of glutamate transmission in VTA, dopamine transmission in dorsolateral striatum, and both dopamine and glutamate transmission in accumbens shell in context-induced reinstatement of heroin seeking (Bossert et al., 2004; Bossert et al., 2006a; Bossert et al., 2007; Bossert et al., 2009). We also showed that projections from ventral mPFC to accumbens shell are critical for this reinstatement (Bossert et al., 2012). We are currently exploring whether projections from ventral subiculum/CA1 to accumbens shell and projections from ventral subiculum/CA1 to ventral mPFC are critical for context-induced reinstatement of heroin seeking.

b. Cocaine

Early studies using the reinstatement procedure have indicated a role for mPFC, BLA, and accumbens core in discriminative- and discrete cue-induced reinstatement of cocaine seeking (Ciccocioppo et al., 2001; Fuchs et al., 2004; McLaughlin and See, 2003). Fuchs and colleagues initially sought to determine whether or not brain areas controlling cue-induced reinstatement of cocaine seeking also control context-induced reinstatement. They found that inactivation (using the sodium channel blocker tetrodotoxin) of dorsal mPFC and BLA, but not ventral mPFC or somatosensory cortex, decreases context-induced reinstatement of cocaine seeking (Fuchs et al., 2005). Because dorsal hippocampus is involved in contextual learning (Holland and Bouton, 1999), they tested whether this brain area also contributes to context-induced reinstatement. They found that inactivation of dorsal hippocampus decreases context- but not discrete cue-induced reinstatement of cocaine seeking (Fuchs et al., 2005). This effect involves local dopamine and glutamate transmission, because injections of dopamine D1-like, mGluR1, and NMDA receptor antagonists all decrease context-induced reinstatement (Xie et al., 2010; Xie et al., 2013; Xie et al., 2014).

In subsequent experiments, these authors found that reversible inactivation (using muscimol + baclofen) of both accumbens core and shell, and dorsolateral striatum, decreases context-induced reinstatement of cocaine seeking (Fuchs et al., 2006; Fuchs et al., 2008). Taken together, the findings of Fuchs, See, and colleagues indicate that while some brain areas (BLA, accumbens core, dorsal mPFC) control both context- and discrete cue-induced reinstatement of cocaine seeking, other brain areas (accumbens shell, dorsal hippocampus) selectively control context-induced reinstatement.

Glutamate transmission in accumbens is critical for discrete cue-induced reinstatement of cocaine, heroin, nicotine, and alcohol seeking (Backstrom and Hyttia, 2007; Kumaresan et al., 2009; LaLumiere and Kalivas, 2008; Liechti et al., 2007; Sinclair et al., 2012). Based on this finding, Fuchs and colleagues examined the contribution of specific glutamate receptor subtypes in accumbens in context-induced reinstatement of cocaine seeking. They found that antagonism of mGluR1 (using JNJ16259685) in accumbens core, but not shell, decreases context-induced reinstatement of cocaine seeking (Xie et al., 2012); antagonism of AMPA/kainite glutamate receptors (using CNQX) in accumbens core and accumbens shell decreases this reinstatement while injections into dorsal striatum were ineffective. The reasons why antagonism of mGluR1 receptors in core but not shell decreases context-induced reinstatement of cocaine seeking is unknown but may be related to distribution of the mGluR1 receptor in these subregions. The involvement of accumbens core in context-induced reinstatement of cocaine seeking is supported by a recent study (Stankeviciute et al., 2013). These authors reported that context-induced reinstatement is associated with a fast, transient increase in spine head diameter of accumbens core neurons. The functional significance of this finding and whether this effect also occurs in accumbens shell is unknown.

Bruce Hope and colleagues used the novel Daun02 method (Koya et al., 2009) to demonstrate that selective inactivation of Fos- and β -galactosidase-expressing neurons in accumbens shell but not core decreases context-induced reinstatement of cocaine seeking

after these neurons were previously activated by exposure to the cocaine-associated context after extinction in the non-drug context (Cruz et al., 2014). In contrast, Daun02 inactivation of neurons that were previously activated by exposure to a novel context (which increases both Fos- and β -galactosidase-expression to levels higher than the cocaine context) had no effect on subsequent context-induced reinstatement. These data are inconsistent with the data from Fuchs and colleagues on the role of accumbens core in context-induced reinstatement (Fuchs et al., 2008; Xie et al., 2012) (see above).

The reason for this discrepancy is not clear, but one possibility is that unlike our studies (see Box 1), Fuchs and colleagues use a renewal procedure in which explicit drug-paired discrete cues are not present during drug self-administration (training), extinction, and reinstatement (Fuchs et al., 2005). This procedural difference is important, because the presence or absence of discrete drug-paired cues can determine whether contexts directly induce drug seeking by acquiring Pavlovian conditioned stimulus properties or indirectly by modulating the effects of discrete infusion cues on drug seeking by serving as occasion setters (Holland, 1992; Rescorla et al., 1985; Urcelay and Miller, 2014). While these two mechanisms are not mutually exclusive (contexts may serve as both traditional Pavlovian conditioned stimuli and occasion setters), they are likely mediated by different neurobiological substrates (Holland and Bouton, 1999). Such differences might account for some discrepancies between Fuchs' studies and the Cruz et al. (2014) study that includes explicitly-paired cues during the training, extinction, and reinstatement test phases.

Because dorsal mPFC, BLA, and dorsal hippocampus have reciprocal connections and project to accumbens (Cassell and Wright, 1986; Sesack et al., 1989; Shinonaga et al., 1994), Fuchs and colleagues examined whether connections among these structures are critical for this reinstatement. Using an asymmetric disconnection procedure (Gold, 1966), they found that contralateral, but not ipsilateral, inactivation of BLA and dorsal hippocampus decreases context-induced reinstatement of cocaine seeking, whereas both contralateral and ipsilateral inactivation of BLA-dorsal mPFC decreases this reinstatement (Fuchs et al., 2007). These findings potentially suggest that a serial interaction exists between BLA and dorsal hippocampus, as well as BLA and dorsal mPFC, in mediating this reinstatement. However, this conclusion should be taken with caution because of the similar effects of contralateral and ipsilateral BLA–dorsal mPFC inactivation.

The asymmetrical disconnection procedure relies on the fact that most neuronal projections are ipsilateral and the assumption that most learned behaviors can be maintained by an intact single hemisphere (but see (Christakou et al., 2005) for data inconsistent with this view). As such, the role a specific projection plays in a given behavior is inferred from the manipulation of one brain area in one hemisphere together with manipulation of a connected brain area in the contralateral hemisphere (Gaffan et al., 1993). Therefore, a main requirement for interpreting results from asymmetrical disconnection studies is that the target behavior remains largely intact after ipsilateral lesion/inactivation of the two brain areas (Setlow et al., 2002). As such, the result of Fuchs et al., (2007) showing that that ipsilateral BLA-dorsal mPFC inactivation decreases reinstatement, suggests that the projection is not critical for reinstatement. However, anatomical studies indicate reciprocal connections between these two structures (McDonald, 1998; Pitkanen, 2000), including

bilateral mPFC projections to amygdala (McDonald et al., 1996). Thus, the results of Fuchs et al., (2007) may not reflect independence of the two brain areas in controlling context-induced reinstatement. Instead, they suggest that unilateral BLA-mPFC activity is not sufficient to maintain normal responding for contexts during reinstatement testing.

BLA also shares reciprocal projections with orbitofrontal cortex (OFC) (Ghashghaei and Barbas, 2002). Inactivation of lateral, but not medial, OFC decreases context-induced reinstatement of cocaine seeking (Lasseter et al., 2009), an effect mimicked by contralateral and ipsilateral disconnection of OFC—BLA projections (Lasseter et al., 2011). Similar to the previous BLA-dorsal mPFC findings, one interpretation of these results is that bilateral input to these structures is required for normal responding during context-induced reinstatement tests, because lateral OFC shares reciprocal connections with BLA. An alternative interpretation is that a third brain area that projects to both structures is also involved in context-induced reinstatement.

A likely candidate is VTA since this brain area sends dopaminergic projections to both BLA and OFC (Oades and Halliday, 1987). Potential support for this idea comes from the findings that blocking dopamine D1-like receptors with SCH 23390 in lateral OFC decreases context-induced reinstatement of cocaine seeking (Lasseter et al., 2014). This effect is mimicked by both contralateral and ipsilateral disconnection of OFC from BLA and is reversed by combining the bilateral OFC SCH 23390 injections with the dopamine D1 agonist SKF 81297. Additionally, the authors used unilateral retrograde tracer injections into OFC or BLA and found evidence for contralateral projections from VTA to OFC, as well as contralateral projections from BLA to OFC and back to BLA from OFC. Taken together, the authors proposed a role for VTA-OFC-BLA in context-induced reinstatement of cocaine seeking. Empirical support for this notion will require simultaneous ‘disconnection’ of all three brain areas, which is technically challenging.

In an elegant study, Luo et al. (2011) combined neuroanatomical tracing, electrophysiology, and pharmacological disconnection techniques to study the role of VTA-lateral septum-dorsal hippocampus circuitry in context-induced reinstatement of cocaine seeking. The authors first found that lateral septum modulates neuronal activity of the projection from dorsal hippocampus CA3 to VTA. They then found that bilateral inactivation of dorsal hippocampus CA3 decreases context-induced reinstatement of cocaine seeking, an effect mimicked by disconnecting lateral septum and contralateral, but not ipsilateral, VTA. Although the authors did not functionally disconnect this pathway (multi-synaptic pharmacological disconnections that alter behavior are technically challenging and difficult to interpret), their findings suggest that neural transmission from dorsal hippocampus CA3 to VTA via lateral septum is a critical pathway for context-induced reinstatement of cocaine seeking.

Lastly, a critical role for ventral hippocampus has recently been reported. Lasseter et al. (2010) found that inactivation of ventral hippocampus, but not posterior dorsal hippocampus or dentate gyrus, decreases context-induced reinstatement of cocaine seeking. Based on previous findings that inactivation of anterior dorsal hippocampus decreases context-induced

reinstatement of cocaine seeking (Fuchs et al., 2005), the negative finding of Lasseter et al. for posterior dorsal hippocampus inactivation are unexpected.

Taken together, dopamine and glutamate transmission in several brain areas and circuits play a role in context-induced reinstatement of cocaine seeking. These include the dorsal mPFC and lateral OFC along with their reciprocal connections with BLA (Fuchs et al., 2005; Fuchs et al., 2007; Lasseter et al., 2011; Lasseter et al., 2014). Striatal areas are also involved in this reinstatement, including dorsolateral striatum and accumbens shell and core (Fuchs et al., 2006; Fuchs et al., 2008; Xie et al., 2012). Finally, both ventral and dorsal hippocampus are involved in context-induced reinstatement of cocaine seeking, and potentially a projection from dorsal hippocampus to VTA via lateral septum (Fuchs et al., 2007; Luo et al., 2011; Xie et al., 2010; Xie et al., 2013; Xie et al., 2014). There is also evidence for a role of the dopaminergic projection from VTA to lateral OFC in context-induced reinstatement of cocaine seeking (Lasseter et al., 2014).

c. Alcohol

Context-induced reinstatement of alcohol seeking was first demonstrated by Burattini et al., (2006). Since then, this behavioral effect has been replicated by several independent investigators (Bossert et al., 2013; McNally, 2014). To date, there are no studies directly implicating a corticostriatal projection in mediating context-induced reinstatement of alcohol seeking. However, several studies have examined the importance of striatal and cortical regions separately.

Nucleus accumbens shell is the main striatal sub-region implicated in context-induced reinstatement of alcohol seeking. Using Fos as a marker of neuronal activity, Hamlin et al. (2007) found that reinstatement of alcoholic beer seeking is associated with increased Fos protein expression in accumbens shell, as well as BLA, and lateral hypothalamus (LH). This effect is dependent on dopamine transmission: systemic injections of the dopamine D1 receptor antagonist SCH 23390 (10 µg/kg) block both context-induced reinstatement and Fos expression in accumbens shell and LH, but not BLA. A critical site for the systemic effect of SCH 23390 is the accumbens shell. Chaudhri et al. (2009) found that SCH 23390 injections into either accumbens shell or core attenuate this reinstatement. Other pharmacological manipulations have also implicated the accumbens shell: local injections of Cocaine and Amphetamine Regulated Transcript (CART) (Millan and McNally, 2012) and the µ-opioid receptor antagonist CTAP (Perry and McNally, 2013) decrease context-induced reinstatement of alcohol seeking.

Chaudhri and colleagues have further described important differences in the role of accumbens shell and core in controlling cue- versus context-induced reinstatement. As reviewed above, Chaudhri et al., (2009) showed that injections of SCH 23390 into either accumbens shell or core decreases context-induced reinstatement of alcohol seeking. In this study, accumbens core was more sensitive to the lower dose (0.06 µg) than accumbens shell, which was only effective at the highest dose tested (0.6 µg). In another study, Chaudhri et al., (2008) found that muscimol+baclofen inactivation of accumbens core, but not shell, decreases context-induced reinstatement of alcohol seeking. However, in this study the rats were given a priming dose of ethanol in both the extinction and training contexts. As such,

this important procedural difference might account for the negative effect of accumbens shell inactivation on alcohol seeking. Chaudhri et al., (2010) further showed the importance of ventral striatal sub-regions in cue- versus context-induced alcohol seeking using a Pavlovian ABA renewal procedure in which a discrete cue is paired with non-contingent alcohol delivery in one context, and the conditioned response to the discrete cue is extinguished in a different context. They found that either accumbens core or shell inactivation (muscimol+baclofen) decreases cue-induced conditioned responding in the original context after Pavlovian extinction in an alternative context (i.e., renewal). However, when the alcohol-associated discrete cue was presented in the extinction context, only accumbens core inactivation decreased the conditioned response; accumbens shell inactivation had no effect. These findings are consistent with the notion that accumbens core being more important for discrete cue-induced reinstatement of drug seeking whereas accumbens shell is more important for context-induced reinstatement.

The role of the projection from mPFC to striatum in context-induced reinstatement of alcohol seeking has not been directly assessed using asymmetrical disconnection or optogenetics. However, dorsal mPFC has been demonstrated to be a critical brain region. Willcocks and McNally (2012) used reversible inactivation (muscimol+baclofen) to demonstrate that dorsal mPFC inactivation decreases context-induced reinstatement of alcohol seeking. Interestingly, there was no effect of reversible inactivation of ventral mPFC, or dorsal peduncular cortex, located ventral to ventral mPFC. To determine which projections to accumbens shell are activated during context-induced relapse, Hamlin et al., (2009) combined Fos expression with retrograde tracer (CTb) injections into the accumbens shell. They found no reinstatement-associated increase of Fos expression in mPFC projections to accumbens shell. Interestingly, the only projection that was analyzed and found significant was the midline thalamic structure paraventricular thalamus (note that ventral subiculum was not analyzed in this study). This highlights the potential importance of the glutamatergic inputs to the striatum from the thalamus, which is an often overlooked projection. Finally, given that both accumbens core (Chaudhri et al., 2009) and dorsal mPFC (Willcocks and McNally, 2012) are critical for context-induced reinstatement of alcohol seeking, it is possible that projections from dorsal mPFC to accumbens core mediate context-induced reinstatement after extinction; however, to date there are no experimental data supporting this hypothesis.

BLA is also important for context-induced reinstatement of alcohol seeking. Both Hamlin et al., (2007) and Marinelli et al., (2007) found increased Fos expression in BLA in rats tested for context-induced reinstatement. While Hamlin et al., (2007) found that blockade of D1-like receptors does not decrease BLA Fos expression, Marinelli et al., (2007) found that systemic injections of the opioid receptor antagonist naltrexone (1 mg/kg) attenuates both reinstatement and Fos expression in BLA. A causal role for the opioid system in context-induced reinstatement of alcohol seeking was subsequently demonstrated by Marinelli et al. (2010). They found that BLA injections of naloxone-methiodide (a charged analogue of the preferential mu opioid receptor antagonist naloxone) dose-dependently decrease context-induced reinstatement of alcohol seeking.

BLA sends dense projections to nucleus accumbens (Kelley et al., 1982; McDonald, 1991). However, there is no evidence to date for a role of this projection in context-induced reinstatement. Millan and McNally (2011) performed an asymmetrical disconnection experiment with BLA injections of muscimol+baclofen and accumbens shell injections of the AMPA receptor antagonist NBQX. They found that this manipulation *induces* reinstatement of extinguished alcohol seeking. This finding is consistent with previous results from this lab showing that bilateral accumbens shell injections of NBQX induce reinstatement of extinguished alcohol seeking (Millan et al., 2010). Millan and McNally (2011) have also showed that NBQX injections into accumbens shell do not decrease context-induced reinstatement of alcohol seeking, but do reinstate alcohol seeking in the extinction context B. This finding suggests a possible dual role for BLA in controlling alcohol seeking. BLA is critical for promoting alcohol seeking in context-induced reinstatement, but it also suppresses alcohol seeking during extinction via projections to accumbens shell.

In summary, like context-induced reinstatement of cocaine and heroin seeking, accumbens shell is a critical neural substrate of context-induced reinstatement of alcohol seeking. BLA is also critical, and this is dependent on activity of opioid receptors in this brain area (Marinelli et al., 2010). The role of glutamate receptors in accumbens shell is more complicated. Glutamatergic inputs to accumbens shell from the midline thalamus are activated during context-induced reinstatement (Hamlin et al., 2009), but a causal role of this projection has not been demonstrated. Projections from BLA to accumbens shell do not appear to play a role in context-induced reinstatement but appear important for suppressing alcohol seeking during extinction; this role is not context dependent (Millan and McNally, 2011).

3. Comparison of corticostriatal inputs in context-induced reinstatement across drug classes

As reviewed above, context-induced reinstatement of drug-seeking is reliably observed in laboratory animals that were trained to self-administer drugs abused by humans. The robustness of this behavioral observation suggests a common psychological mechanism is responsible for context-induced reinstatement (Crombag et al., 2008). However, despite the observed behavior being identical (i.e. increased operant responding during the reinstatement test), there is emerging evidence that the neural substrates of context-induced reinstatement across drug classes are not identical. In this section we review the neurobiological similarities and differences of the corticostriatal mechanisms of context-induced reinstatement for heroin, cocaine, and alcohol seeking.

Nucleus accumbens shell stands out for being consistently implicated in context-induced reinstatement across drug and non-drug rewards. Increased Fos in accumbens shell is associated with context-induced reinstatement of sucrose (Hamlin et al., 2006), alcohol (Hamlin et al., 2007), and cocaine (Cruz et al., 2014) seeking. Antagonism of dopamine D1-like receptors in accumbens shell attenuates context-induced reinstatement of both alcohol and heroin seeking (Bossert et al., 2007; Chaudhri et al., 2009). Antagonism of glutamate receptors in accumbens shell blocks context-induced reinstatement of cocaine seeking

(Fuchs et al., 2008; Xie et al., 2012) and suppression of glutamate transmission through activation of mGluR2/3 receptors attenuates context-induced reinstatement of heroin seeking (Bossert et al., 2006a). Finally, selective inactivation of the reinstatement-associated Fos neurons in accumbens shell, using the Daun02 inactivation procedure (Koya et al., 2009), attenuates context-induced reinstatement of cocaine seeking (Cruz et al., 2014).

One possible reason that accumbens shell is critical for reinstatement induced by drug-context associations is because it receives strong projections from ventral hippocampus, which has been demonstrated to be critical for context-induced reinstatement of both heroin and cocaine seeking (Bossert and Stern, 2014; Lasseter et al., 2010). Interestingly, using optogenetics to measure the synaptic strength of different accumbens shell projections, Britt et al. (2012) found that synaptic currents induced by optical stimulation of ventral hippocampus projections to accumbens shell are stronger than BLA or mPFC projections. As such, it is possible that the conserved role of accumbens shell in mediating context-induced reinstatement across multiple drug types is driven in part by strong inputs from ventral hippocampus, which are presumably conveying the motivational significance of the drug-associated contexts.

One of the main differences that have emerged in the literature reviewed above is that context-induced reinstatement of different classes of drugs is mediated by different sub-regions of mPFC and the corresponding projections to nucleus accumbens. Reversible inactivation of dorsal, but not ventral, mPFC decreases context-induced reinstatement of alcohol or cocaine seeking (Fuchs et al., 2005; Willcocks and McNally, 2012). In contrast, reversible inactivation of ventral, but not dorsal, mPFC attenuates context-induced reinstatement of heroin seeking (Bossert et al., 2011). Additionally, Peters et al. (2008) have shown that extinguished cocaine seeking is reinstated by reversible inactivation of ventral but not dorsal mPFC. This effect was shown to be dependent on accumbens shell, because reinstatement induced by unilateral inactivation of ventral mPFC was increased when the ipsilateral or contralateral accumbens shell was also inactivated. In contrast, this inhibitory role of the ventral mPFC to accumbens shell projection is not seen in rats trained to self-administer heroin. Bossert et al., (2012) have shown that disconnection of ventral mPFC (muscimol+baclofen) and accumbens shell (D1-like receptor antagonist) decreases context-induced reinstatement of heroin seeking; this manipulation has no effect on extinction responding. Taken together, these findings demonstrate that there are significant differences in the corticostriatal control over context-induced cocaine, heroin, and alcohol seeking.

An important consideration towards understanding the conflicting data on mPFC projections to nucleus accumbens is the overlapping projections of ventral and dorsal mPFC to the nucleus accumbens. An influential review article from Peters et al. (2009) proposed behaviorally opposite roles for dorsal and ventral mPFC projections to accumbens core and shell, respectively. They proposed that dorsal mPFC to accumbens core projections promote drug seeking while ventral mPFC to accumbens shell projections inhibit drug seeking. While there is some evidence for this dichotomy in the case of cocaine seeking (Peters et al., 2008), a close examination of the original anatomical studies describing the mPFC projections to nucleus accumbens shows that the anatomical evidence does not support this kind of parallel circuitry. Both retrograde (Brog et al., 1993) and anterograde (Sesack et al., 1989) tracing

studies show that accumbens core receives dense projections from both ventral and dorsal mPFC. As such, a potentially important consideration that is overlooked is the extent to which ventral mPFC projections to accumbens core contributes to the promotion or inhibition (as in extinction) of drug seeking.

Conclusions and future directions

The data reviewed above show there are significant similarities (accumbens shell, ventral hippocampus, BLA) and differences (mPFC and its projections to accumbens) in the neural mechanisms of context-induced reinstatement of heroin, cocaine, and alcohol seeking. The extent to which the different experimental parameters used in different laboratories (Box 1) accounts for these results is not known (Crombag et al., 2008). Unfortunately, there are no studies specifically examining these differences in a single experiment with different groups of rats trained to self-administer heroin, cocaine, or alcohol. Procedural differences aside, as discussed previously (Badiani et al., 2011), we propose that one potential contributing factor for these differences is the different motivational states induced by these drugs. There is a large body of evidence showing that different drug-induced motivational states are mediated by different neural substrates (Badiani et al., 2011; Badiani, 2013; Caprioli et al., 2007; Ettenberg, 2004; Ettenberg, 2009). As such, we speculate that different drug-associated contexts induce drug seeking through different mechanisms because of the unique motivational state each drug induces.

Finally, we have recently developed an alternative renewal procedure to study context-induced relapse to alcohol seeking after suppression of alcohol taking by adverse consequences (Marchant et al., 2013a). We developed this procedure because as has been noted in the literature, extinction does not adequately capture the motivation for abstinence in humans (Epstein et al., 2006; Katz and Higgins, 2003; Marlatt, 2002; Tiffany and Conklin, 2002). Rather, in humans abstinence is typically self-imposed despite drug availability, often out of a desire to avoid the negative consequences associated with excessive drug use (Burman, 1997; Klingemann, 1991).

To model this phenomenon, we used response-contingent punishment, with electric foot-shock, in place of extinction to suppress alcohol taking in context B. Importantly, we found that the footshock must be contingent on alcohol-reinforced lever pressing to suppress alcohol taking. Rats that received non-contingent foot-shock during context B self-administration do not suppress alcohol intake, or alcohol seeking on test in either context A or B. After punishment-imposed abstinence in context B, the observed behavior on test is similar to that seen in context-induced reinstatement after extinction (Marchant et al., 2013a). We found suppressed alcohol seeking in context B, in the absence of foot-shock, and renewed alcohol seeking on test in context A. Given the similarities in the behavioral profile of the two procedures, our main question moving forward is whether the neural mechanisms of context-induced reinstatement after punishment versus after extinction are different (Marchant et al., 2013b). In short, does it matter if drug seeking is suppressed by extinction or adverse consequences?

We recently published our first attempt at characterizing the neural mechanisms of context-induced reinstatement of alcohol seeking after punishment-imposed abstinence (Marchant et al., 2014). We found that this reinstatement is associated with increased Fos expression in lateral hypothalamus (LH) neurons, and that LH neuronal activity is necessary because reversible inactivation (muscimol+baclofen) decreased context-induced reinstatement. Both increased LH Fos expression, and a necessary role for LH neuronal activation have previously been shown for context-induced reinstatement after extinction (Hamlin et al., 2007; Marchant et al., 2009). As such, at least for the role of LH in context-induced reinstatement of alcohol seeking, the procedure used to suppress alcohol seeking (extinction or punishment) does not change the subsequent neural mechanisms of context-induced reinstatement. In addition, context-induced reinstatement after either extinction or punishment is associated with increased Fos expression in accumbens shell neurons that project to LH (Marchant et al., 2009; Marchant et al., 2014). This suggests that LH is a critical output target of accumbens shell that is associated with context-induced alcohol seeking, regardless of the mechanism used to suppress alcohol seeking. In the context of our review, an important question for future research is whether the corticostriatal circuits described above mediate context-induced reinstatement of drug seeking after punishment-imposed abstinence.

Box 1

Glossary of terms

Asymmetrical disconnection procedure (also called the “asymmetric” lesion/inactivation procedure: (Gold, 1966): In this procedure the role of a neuronal pathway in a given behavior is inferred from the observation that lesion (permanent or reversible) or receptor blockade of one brain site in one hemisphere, together with lesion/receptor blockade of a second brain site in the contralateral hemisphere, disrupts the behavior of interest (Gaffan et al., 1993; Setlow et al., 2002). Basic assumptions in “disconnection” studies are that the target behavior is at least partially intact following ipsilateral lesion/inactivation of the two brain sites in the same hemisphere and that neuronal projections are exclusively or primarily ipsilateral.

Contexts: Refers to a configuration of diffuse cues providing the background setting of learning. Investigations on context effects in learning indicate that many stimuli can function as contexts, including external cues like smells and physical environments, interceptive drug states, mood or hormonal states, and time of day (Bouton, 1993).

Context-induced reinstatement: Laboratory animals are first trained to self-administer a drug in an environment (termed context A) associated with a specific set of “background” stimuli (e.g., operant chamber fan, time of day, visual cues, tactile cues, olfactory cues). Lever pressing is then extinguished in a different environment (termed context B) with a different set of “background” stimuli. During reinstatement testing under extinction conditions, exposure to context A previously paired with the drug reinstates operant responding. The procedure is based on a “renewal” procedure that has been used to assess the role of contexts in resumption of conditioned responses to aversive and appetitive cues after extinction (Bouton and Swartzentruber, 1991). Note

that there are two versions of context-induced reinstatement: (1) Discrete drug cues are present during training, extinction, and reinstatement (Crombag and Shaham, 2002); in this procedure, contexts may indirectly induce drug seeking by modulating the effects of discrete infusion cues on drug seeking by serving as occasion setters; (2) Discrete cues are absent during training, extinction, and reinstatement (Fuchs et al., 2005); in this procedure, contexts may directly induce drug seeking by acquiring Pavlovian conditioned stimulus properties.

Context-induced relapse after punishment: This procedure is similar to context-induced reinstatement with the exception that in context B pressing the active lever results in drug delivery and footshock punishment. The footshock punishment occurs at the same time as alcohol delivery, but only 50% of reinforced lever presses are punished. Alcohol seeking remains suppressed in the punishment context (B), but renews during the relapse tests in the alcohol context (A) (Marchant et al., 2013a; Marchant et al., 2013b). (Marchant et al., 2014)

Daun02 inactivation procedure: A method to selectively disrupt the function of behaviorally activated neurons. This method enables investigation of whether “neuronal ensembles” (subsets of activated neurons) are involved in particular behaviors. Selective inactivation is performed by injecting a prodrug, Daun02 into the brains of c-fos-lacZ transgenic rats that express beta-galactosidase in strongly activated neurons. Beta-galactosidase converts Daun02 into daunorubicin, which reduces neuronal excitability (Koya et al., 2009).

Discrete cue-induced reinstatement: Laboratory animals are first trained to self-administer a drug; each drug delivery is temporally paired with a discrete cue (e.g., tone, light). Lever pressing is then extinguished in the absence of the drug and the cue. During reinstatement testing, exposure to the discrete cue, which is earned contingently during testing, reinstates responding (Meil and See, 1996b).

Discriminative cue-induced reinstatement: Laboratory animals are trained to self-administer a drug in the presence of distinct discriminative stimuli (e.g., visual cues, olfactory cues); one set of stimuli signals drug availability (S+) and the other signals unavailability (S–). Lever pressing is then extinguished in the absence of the discriminative stimuli and the drug. During the reinstatement test, re-exposure to the S+, but not S–, reinstates operant responding (Weiss et al., 2000).

Occasion setter cue: In Pavlovian conditioning occasion setter cues signal whether another conditioned cue (CS) is to be reinforced or not reinforced. In contrast to traditional excitatory or inhibitory Pavlovian CSs, occasion setter cues typically do not affect behavior directly but modulate behavior elicited by other Pavlovian CSs (Holland, 1992).

Reinstatement: In the learning literature, reinstatement refers to the recovery of a learned response (e.g., lever-pressing behavior) that occurs when a subject is exposed non-contingently to the unconditioned stimulus (e.g., food) after extinction (Bouton and Swartzentruber, 1991). In studies of reinstatement of drug-seeking, reinstatement typically refers to the resumption of drug seeking after extinction following exposure to

drugs (de Wit and Stewart, 1981; Self et al., 1996; Spealman et al., 1999), different types of drug cues (Crombag and Shaham, 2002; Meil and See, 1996a; Weiss et al., 2000), or different stressors (Shaham and Stewart, 1995; Shalev et al., 2001).

Relapse: A term used to describe the resumption of drug-taking behavior during self-imposed or forced abstinence in humans (Wikler, 1973).

Renewal: Refers to the recovery of extinguished conditioned behavior that can occur when the context is changed after extinction; renewal often occurs when the subject returns to the learning (training) environment after extinction of the conditioned response in a different environment (Bouton and Swartzentruber, 1991).

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Abbreviations

Brain areas:

BLA	basolateral amygdala
CA1	field CA1 of the hippocampus
CA3	field CA3 of the hippocampus
DHipp	dorsal hippocampus
dlStr	dorsolateral striatum
dmPFC	dorsomedial prefrontal cortex
dmStr	dorsomedial striatum
dStriatum	dorsal striatum
dSub	dorsal subiculum
IOFC	lateral orbitofrontal cortex
IShell	lateral nucleus accumbens shell
mOFC	medial orbitofrontal cortex
NAc Core	nucleus accumbens core
NAc Shell	nucleus accumbens shell
OFC	orbitofrontal cortex
pDHipp	posterior dorsal hippocampus
vCPu	ventral caudate putamen
VHipp	ventral hippocampus

vmPFC	ventromedial prefrontal cortex
vSub	ventral subiculum
VTA	ventral tegmental area
Drugs:	
AP5	NMDA receptor antagonist
CART	Cocaine and Amphetamine Regulated Transcript
CNQX	AMPA/kainate receptor antagonist
CTAP	μ -opioid receptor antagonist
JNJ16259685	mGluR1-selective antagonist
LY379268	mGluR _{2/3} agonist
M+B	Muscimol + Baclofen (GABA _A and GABA _B receptor agonists, respectively)
Naloxone-methiodide	a charged analogue of naloxone (a preferential mu opioid receptor antagonist)
PP2	Src-family kinase inhibitor
Ro25-6981	NR2B subunit-containing NMDAR antagonist
SCH 23390	Dopamine D1-like receptor antagonist
TTX	tetrodotoxin (tetrodotoxin-sensitive voltage-gated sodium channel blocker)

References

- Backstrom P, Hyytia P. Involvement of AMPA/kainate, NMDA, and mGlu5 receptors in the nucleus accumbens core in cue-induced reinstatement of cocaine seeking in rats. *Psychopharmacology*. 2007; 192:571–580. [PubMed: 17347848]
- Badiani A, Belin D, Epstein DH, Calu DJ, Shaham Y. Opiate versus psychostimulant addiction: the differences do matter. *Nat Rev Neurosci*. 2011; 12:685–700. [PubMed: 21971065]
- Badiani A. Substance-specific environmental influences on drug use and drug preference in animals and humans. *Curr Opin Neurobiol*. 2013; 23:588–96. [PubMed: 23622777]
- Baptista MA, Martin-Fardon R, Weiss F. Preferential effects of the metabotropic glutamate 2/3 receptor agonist LY379268 on conditioned reinstatement versus primary reinforcement: comparison between cocaine and a potent conventional reinforcer. *J. Neurosci*. 2004; 24:4723–4727. [PubMed: 15152032]
- Beckstead RM, Domesick VB, Nauta WJ. Efferent connections of the substantia nigra and ventral tegmental area in the rat. *Brain Res*. 1979; 175:191–217. [PubMed: 314832]
- Bossert JM, Liu SY, Lu L, Shaham Y. A role of ventral tegmental area glutamate in contextual cue-induced relapse to heroin seeking. *J. Neurosci*. 2004; 24:10726–10730. [PubMed: 15564590]
- Bossert JM, Busch RF, Gray SM. The novel mGluR2/3 agonist LY379268 attenuates cue-induced reinstatement of heroin seeking. *Neuroreport*. 2005; 16:1013–1016. [PubMed: 15931079]
- Bossert JM, Gray SM, Lu L, Shaham Y. Activation of group II metabotropic glutamate receptors in the nucleus accumbens shell attenuates context-induced relapse to heroin seeking. *Neuropsychopharmacology*. 2006a; 31:2197–2209. [PubMed: 16341024]

- Bossert JM, Poles GC, Sheffler-Collins SI, Ghitza UE. The mGluR2/3 agonist LY379268 attenuates context- and discrete cue-induced reinstatement of sucrose seeking but not sucrose self-administration in rats. *Behav. Brain Res.* 2006b; 173:148–152. [PubMed: 16834996]
- Bossert JM, Poles GC, Wihbey KA, Koya E, Shaham Y. Differential effects of blockade of dopamine D1-family receptors in nucleus accumbens core or shell on reinstatement of heroin seeking induced by contextual and discrete cues. *J. Neurosci.* 2007; 27:12655–12663. [PubMed: 18003845]
- Bossert JM, Wihbey KA, Pickens CL, Nair SG, Shaham Y. Role of dopamine D(1)-family receptors in dorsolateral striatum in context-induced reinstatement of heroin seeking in rats. *Psychopharmacology.* 2009; 206:51–60. [PubMed: 19506837]
- Bossert JM, Stern AL, Theberge FR, Cifani C, Koya E, Hope BT, Shaham Y. Ventral medial prefrontal cortex neuronal ensembles mediate context-induced relapse to heroin. *Nat. Neurosci.* 2011; 14:420–422. [PubMed: 21336273]
- Bossert JM, Stern AL, Theberge FR, Marchant NJ, Wang HL, Morales M, Shaham Y. Role of projections from ventral medial prefrontal cortex to nucleus accumbens shell in context-induced reinstatement of heroin seeking. *J. Neurosci.* 2012; 32:4982–4891. [PubMed: 22492053]
- Bossert JM, Marchant NJ, Calu DJ, Shaham Y. The reinstatement model of drug relapse: recent neurobiological findings, emerging research topics, and translational research. *Psychopharmacology.* 2013; 229:453–476. [PubMed: 23685858]
- Bossert JM, Stern AL. Role of ventral subiculum in context-induced reinstatement of heroin seeking in rats. *Addict. Biol.* 2014; 19:338–342. [PubMed: 23231571]
- Bouton ME, Bolles RC. Role of conditioned contextual stimuli in reinstatement of extinguished fear. *J. Exp. Psychol. Anim. Behav. Process.* 1979; 5:368–378. [PubMed: 528893]
- Bouton ME, Swartzentruber D. Sources of relapse after extinction in Pavlovian and instrumental learning. *Clin. Psychol. Rev.* 1991; 11:123–140.
- Bouton ME. Context, time, and memory retrieval in the interference paradigms of Pavlovian learning. *Psychol. Bull.* 1993; 114:80–99. [PubMed: 8346330]
- Bouton ME. Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. *Biol. Psychiatry.* 2002; 52:976–986. [PubMed: 12437938]
- Britt JP, Benaliouad F, McDevitt RA, Stuber GD, Wise A, Bonci A. Synaptic and Behavioral Profile of Multiple Glutamatergic Inputs to the Nucleus Accumbens. *Neuron.* 2012; 76:790–803. [PubMed: 23177963]
- Brog JS, Salyapongse A, Deutch AY, Zahm DS. The patterns of afferent innervation of the core and shell in the "Accumbens" part of the rat ventral striatum: Immunohistochemical detection of retrogradely transported fluoro-gold. *The Journal of Comparative Neurology.* 1993; 338:255–278. [PubMed: 8308171]
- Burattini C, Gill TM, Aicardi G, Janak PH. The ethanol self-administration context as a reinstatement cue: acute effects of naltrexone. *Neuroscience.* 2006; 139:877–887. [PubMed: 16516392]
- Burman S. The challenge of sobriety: Natural recovery without treatment and self-help groups. *J. Substance Abuse.* 1997; 9:41–61.
- Caprioli D, Celentano M, Paolone G, Badiani A. Modeling the role of environment in addiction. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* 2007; 31:1639–53. [PubMed: 17889978]
- Cassell MD, Wright DJ. Topography of projections from the medial prefrontal cortex to the amygdala in the rat. *Brain Res. Bull.* 1986; 17:321–333. [PubMed: 2429740]
- Chaudhri N, Sahuque LL, Cone JJ, Janak PH. Reinstated ethanol-seeking in rats is modulated by environmental context and requires the nucleus accumbens core. *Eur. J. Neurosci.* 2008; 28:2288–2298. [PubMed: 19046372]
- Chaudhri N, Sahuque LL, Janak PH. Ethanol seeking triggered by environmental context is attenuated by blocking dopamine D1 receptors in the nucleus accumbens core and shell in rats. *Psychopharmacology.* 2009; 207:303–314. [PubMed: 19779700]
- Chaudhri N, Sahuque LL, Schairer WW, Janak PH. Separable roles of the nucleus accumbens core and shell in context- and cue-induced alcohol-seeking. *Neuropsychopharmacology.* 2010; 35:783–791. [PubMed: 19924113]

- Christakou A, Robbins TW, Everitt BJ. Prolonged neglect following unilateral disruption of a prefrontal cortical-dorsal striatal system. *Eur. J. Neurosci.* 2005; 21:782–792. [PubMed: 15733096]
- Ciccocioppo R, Sanna PP, Weiss F. Cocaine-predictive stimulus induces drug-seeking behavior and neural activation in limbic brain regions after multiple months of abstinence: reversal by D(1) antagonists. *Proc. Natl. Acad. Sci. U. S. A.* 2001; 98:1976–81. [PubMed: 11172061]
- Crombag HS, Grimm JW, Shaham Y. Effect of dopamine receptor antagonists on renewal of cocaine seeking by reexposure to drug-associated contextual cues. *Neuropsychopharmacology.* 2002; 27:1006–1015. [PubMed: 12464457]
- Crombag HS, Shaham Y. Renewal of drug seeking by contextual cues after prolonged extinction in rats. *Behav. Neurosci.* 2002; 116:169–173. [PubMed: 11895178]
- Crombag HS, Bossert JM, Koya E, Shaham Y. Review. Context-induced relapse to drug seeking: a review. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 2008; 363:3233–3243. [PubMed: 18640922]
- Cruz FC, Babin KR, Leao RM, Goldart EM, Bossert JM, Shaham Y, Hope BT. Role of Nucleus Accumbens Shell Neuronal Ensembles in Context-Induced Reinstatement of Cocaine-Seeking. *The Journal of Neuroscience.* 2014; 34:7437–7446. [PubMed: 24872549]
- de Wit H, Stewart J. Reinstatement of cocaine-reinforced responding in the rat. *Psychopharmacology.* 1981; 75:134–143. [PubMed: 6798603]
- de Wit H, Stewart J. Drug reinstatement of heroin-reinforced responding in the rat. *Psychopharmacology.* 1983; 79:29–31. [PubMed: 6403961]
- Diergaarde L, de Vries W, Raaso H, Schoffelmier AN, De Vries TJ. Contextual renewal of nicotine seeking in rats and its suppression by the cannabinoid-1 receptor antagonist Rimonabant (SR141716A). *Neuropharmacology.* 2008; 55:712–716. [PubMed: 18588903]
- Epstein DH, Preston KL, Stewart J, Shaham Y. Toward a model of drug relapse: an assessment of the validity of the reinstatement procedure. *Psychopharmacology.* 2006; 189:1–16. [PubMed: 17019567]
- Ettenberg A. Opponent process properties of self-administered cocaine. *Neurosci. Biobehav. Rev.* 2004; 27:721–8. [PubMed: 15019422]
- Ettenberg A. The runway model of drug self-administration. *Pharmacol. Biochem. Behav.* 2009; 91:271–7. [PubMed: 19032964]
- Fallon JH, Moore RY. Catecholamine innervation of the basal forebrain. IV. Topography of the dopamine projection to the basal forebrain and neostriatum. *J. Comp. Neurol.* 1978; 180:545–580. [PubMed: 659674]
- Fuchs RA, Evans KA, Parker MC, See RE. Differential involvement of the core and shell subregions of the nucleus accumbens in conditioned cue-induced reinstatement of cocaine seeking in rats. *Psychopharmacology.* 2004; 176:459–465. [PubMed: 15138757]
- Fuchs RA, Evans KA, Ledford CC, Parker MP, Case JM, Mehta RH, See RE. The role of the dorsomedial prefrontal cortex, basolateral amygdala, and dorsal hippocampus in contextual reinstatement of cocaine seeking in rats. *Neuropsychopharmacology.* 2005; 30:296–309. [PubMed: 15483559]
- Fuchs RA, Branham RK, See RE. Different neural substrates mediate cocaine seeking after abstinence versus extinction training: a critical role for the dorsolateral caudate-putamen. *J. Neurosci.* 2006; 26:3584–3588. [PubMed: 16571766]
- Fuchs RA, Eaddy JL, Su ZI, Bell GH. Interactions of the basolateral amygdala with the dorsal hippocampus and dorsomedial prefrontal cortex regulate drug context-induced reinstatement of cocaine-seeking in rats. *Eur. J. Neurosci.* 2007; 26:487–498. [PubMed: 17650119]
- Fuchs RA, Ramirez DR, Bell GH. Nucleus accumbens shell and core involvement in drug context-induced reinstatement of cocaine seeking in rats. *Psychopharmacology.* 2008; 200:545–556. [PubMed: 18597075]
- Gaffan D, Murray EA, Fabre-Thorpe M. Interaction of the amygdala with the frontal lobe in reward memory. *Eur. J. Neurosci.* 1993; 5:968–975. [PubMed: 8281307]
- Geisler S, Derst C, Veh RW, Zahm DS. Glutamatergic afferents of the ventral tegmental area in the rat. *J. Neurosci.* 2007; 27:5730–5743. [PubMed: 17522317]

- Ghashghaei HT, Barbas H. Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. *Neuroscience*. 2002; 115:1261–1279. [PubMed: 12453496]
- Ghitza UE, Fabbriatore AT, Prokopenko V, Pawlak AP, West MO. Persistent cue-evoked activity of accumbens neurons after prolonged abstinence from self-administered cocaine. *J. Neurosci*. 2003; 23:7239–7245. [PubMed: 12917356]
- Gold RM. Aphagia and adipsia produced by unilateral hypothalamic lesions in rats. *Am. J. Physiol*. 1966; 211:1274–1276. [PubMed: 5924054]
- Greenslade RG, Mitchell SN. Selective action of (-)-2-oxa-4-aminobicyclo[3.1.0]hexane-4,6-dicarboxylate (LY379268), a group II metabotropic glutamate receptor agonist, on basal and phencyclidine-induced dopamine release in the nucleus accumbens shell. *Neuropharmacology*. 2004; 47:1–8. [PubMed: 15165829]
- Groenewegen HJ, Vermeulen-Van der Zee E, te Kortschot A, Witter MP. Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of Phaseolus vulgaris leucoagglutinin. *Neuroscience*. 1987; 23:103–120. [PubMed: 3683859]
- Groenewegen HJ, Wright CI, Beijer AV, Voorn P. Convergence and segregation of ventral striatal inputs and outputs. *Ann. N. Y. Acad. Sci*. 1999; 877:49–63. [PubMed: 10415642]
- Hamlin AS, Blatchford KE, McNally GP. Renewal of an extinguished instrumental response: neural correlates and the role of D1 dopamine receptors. *Neuroscience*. 2006; 143:25–38. [PubMed: 16949214]
- Hamlin AS, Newby J, McNally GP. The neural correlates and role of D1 dopamine receptors in renewal of extinguished alcohol-seeking. *Neuroscience*. 2007; 146:525–536. [PubMed: 17360123]
- Hamlin AS, Clemens KJ, McNally GP. Renewal of extinguished cocaine-seeking. *Neuroscience*. 2008; 151:659–670. [PubMed: 18164822]
- Hamlin AS, Clemens KJ, Choi EA, McNally GP. Paraventricular thalamus mediates context-induced reinstatement (renewal) of extinguished reward seeking. *Eur. J. Neurosci*. 2009; 29:802–812. [PubMed: 19200064]
- Holland, PC. Occasion setting in Pavlovian conditioning. In: Medlin, DL., editor. *The psychology of learning and motivation*. Academic Press; San Diego, CA: 1992. p. 69-125.
- Holland PC, Bouton ME. Hippocampus and context in classical conditioning. *Curr. Opin. Neurobiol*. 1999; 9:195–202. [PubMed: 10322181]
- Hunt WA, Barnett LW, Branch LG. Relapse rates in addiction programs. *J Clin Psychol*. 1971; 27:455–6. [PubMed: 5115648]
- Katz JL, Higgins ST. The validity of the reinstatement model of craving and relapse to drug use. *Psychopharmacology*. 2003; 168:21–30. [PubMed: 12695875]
- Kelley AE, Domesick VB, Nauta WJ. The amygdalostratial projection in the rat--an anatomical study by anterograde and retrograde tracing methods. *Neuroscience*. 1982; 7:615–30. [PubMed: 7070669]
- Klingemann HKH. The motivation for change from problem alcohol and heroin use. *British J. Addiction*. 1991; 86:727–744.
- Koya E, Golden SA, Harvey BK, Guez-Barber DH, Berkow A, Simmons DE, Bossert JM, Nair SG, Uejima JL, Marin MT, et al. Targeted disruption of cocaine-activated nucleus accumbens neurons prevents context-specific sensitization. *Nat. Neurosci*. 2009; 12:1069–1073. [PubMed: 19620976]
- Kumaresan V, Yuan M, Yee J, Famous KR, Anderson SM, Schmidt HD, Pierce RC. Metabotropic glutamate receptor 5 (mGluR5) antagonists attenuate cocaine priming- and cue-induced reinstatement of cocaine seeking. *Behav. Brain Res*. 2009; 202:238–244. [PubMed: 19463707]
- LaLumiere RT, Kalivas PW. Glutamate release in the nucleus accumbens core is necessary for heroin seeking. *J. Neurosci*. 2008; 28:3170–317. [PubMed: 18354020]
- Lasseter HC, Ramirez DR, Xie X, Fuchs RA. Involvement of the lateral orbitofrontal cortex in drug context-induced reinstatement of cocaine-seeking behavior in rats. *Eur. J. Neurosci*. 2009; 30:1370–1381. [PubMed: 19769591]

- Lasseter HC, Xie X, Ramirez DR, Fuchs RA. Sub-region specific contribution of the ventral hippocampus to drug context-induced reinstatement of cocaine-seeking behavior in rats. *Neuroscience*. 2010; 171:830–839. [PubMed: 20870011]
- Lasseter HC, Wells AM, Xie X, Fuchs RA. Interaction of the basolateral amygdala and orbitofrontal cortex is critical for drug context-induced reinstatement of cocaine-seeking behavior in rats. *Neuropsychopharmacology*. 2011; 36:711–720. [PubMed: 21124303]
- Lasseter HC, Xie X, Arguello AA, Wells AM, Hodges MA, Fuchs RA. Contribution of a mesocorticolimbic subcircuit to drug context-induced reinstatement of cocaine-seeking behavior in rats. *Neuropsychopharmacology*. 2014; 39:660–669. [PubMed: 24051899]
- Liechti ME, Lhuillier L, Kaupmann K, Markou A. Metabotropic glutamate 2/3 receptors in the ventral tegmental area and the nucleus accumbens shell are involved in behaviors relating to nicotine dependence. *J. Neurosci*. 2007; 27:9077–9085. [PubMed: 17715344]
- Luo AH, Tahsili-Fahadan P, Wise RA, Lupica CR, Aston-Jones G. Linking context with reward: a functional circuit from hippocampal CA3 to ventral tegmental area. *Science*. 2011; 333:353–357. [PubMed: 21764750]
- Manzoni OJ, Williams JT. Presynaptic regulation of glutamate release in the ventral tegmental area during morphine withdrawal. *J. Neurosci*. 1999; 19:6629–6636. [PubMed: 10414991]
- Marchant NJ, Hamlin AS, McNally GP. Lateral hypothalamus is required for context-induced reinstatement of extinguished reward seeking. *J. Neurosci*. 2009; 29:1331–1342. [PubMed: 19193880]
- Marchant NJ, Khuc TN, Pickens CL, Bonci A, Shaham Y. Context-Induced Relapse to Alcohol Seeking After Punishment in a Rat Model. *Biol. Psychiatry*. 2013a; 73:256–262. [PubMed: 22883434]
- Marchant NJ, Li X, Shaham Y. Recent developments in animal models of drug relapse. *Curr Opin Neurobiol*. 2013b; 23:675–83. [PubMed: 23374536]
- Marchant NJ, Rabe R, Kaganovsky K, Caprioli D, Bossert JM, Bonci A, Shaham Y. A Critical Role of Lateral Hypothalamus in Context-Induced Relapse to Alcohol Seeking after Punishment-Imposed Abstinence. *The Journal of Neuroscience*. 2014; 34:7447–7457. [PubMed: 24872550]
- Marinelli PW, Funk D, Juzysch W, Li Z, Le AD. Effects of opioid receptor blockade on the renewal of alcohol seeking induced by context: relationship to c-fos mRNA expression. *Eur. J. Neurosci*. 2007; 26:2815–2823. [PubMed: 18001278]
- Marinelli PW, Funk D, Juzysch W, Le AD. Opioid receptors in the basolateral amygdala but not dorsal hippocampus mediate context-induced alcohol seeking. *Behav. Brain Res*. 2010; 211:58–63. [PubMed: 20214927]
- Marlatt GA. Do animal models provide a valid analogue for human drug lapse and relapse? Comment on Leri and Stewart (2002). *Exp. Clin. Psychopharmacol*. 2002; 10:359–360. [PubMed: 12498331]
- McDonald AJ. Topographical organization of amygdaloid projections to the caudatoputamen, nucleus accumbens, and related striatal-like areas of the rat brain. *Neuroscience*. 1991; 44:15–33. [PubMed: 1722890]
- McDonald AJ, Mascagni F, Guo L. Projections of the medial and lateral prefrontal cortices to the amygdala: a Phaseolus vulgaris leucoagglutinin study in the rat. *Neuroscience*. 1996; 71:55–75. [PubMed: 8834392]
- McDonald AJ. Cortical pathways to the mammalian amygdala. *Prog. Neurobiol*. 1998; 55:257–332. [PubMed: 9643556]
- McFarland K, Ettenberg A. Reinstatement of drug-seeking behavior produced by heroin-predictive environmental stimuli. *Psychopharmacology*. 1997; 131:86–92. [PubMed: 9181640]
- McLaughlin J, See RE. Selective inactivation of the dorsomedial prefrontal cortex and the basolateral amygdala attenuates conditioned-cued reinstatement of extinguished cocaine-seeking behavior in rats. *Psychopharmacology*. 2003; 168:57–65. [PubMed: 12845418]
- McNally GP. Extinction of drug seeking: Neural circuits and approaches to augmentation. *Neuropharmacology*. 2014; 76:528–32. Pt B. [PubMed: 23774135]
- Meil WM, See RE. Conditioned cued recovery of responding following prolonged withdrawal from self-administered cocaine in rats: an animal model of relapse. *Behav. Pharmacol*. 1996a; 7:754–763. [PubMed: 11224470]

- Meil WM, See RE. Conditioned cued recovery of responding following prolonged withdrawal from self-administered cocaine in rats: an animal model of relapse. *Behav. Pharmacol.* 1996b; 7:754–763. [PubMed: 11224470]
- Millan EZ, Furlong TM, McNally GP. Accumbens Shell-Hypothalamus Interactions Mediate Extinction of Alcohol Seeking. *J. Neurosci.* 2010; 30:4626–4635. [PubMed: 20357113]
- Millan EZ, McNally GP. Accumbens shell AMPA receptors mediate expression of extinguished reward seeking through interactions with basolateral amygdala. *Learn. Mem.* 2011; 18:414–421. [PubMed: 21677189]
- Millan EZ, McNally GP. Cocaine- and amphetamine-regulated transcript in the nucleus accumbens shell attenuates context-induced reinstatement of alcohol seeking. *Behav. Neurosci.* 2012; 126:690–698. [PubMed: 23025832]
- Morgan JI, Curran T. Stimulus-transcription coupling in the nervous system: involvement of the inducible proto-oncogenes fos and jun. *Annu. Rev. Neurosci.* 1991; 14:421–451. [PubMed: 1903243]
- Nakajima S, Tanaka S, Urushihara K, Imada H. Renewal of Extinguished Lever-Press Responses upon Return to the Training Context. *Learning and Motivation.* 2000; 31:416–431.
- O'Brien CP, Childress AR, McLellan AT, Ehrman R. Classical conditioning in drug-dependent humans. *Ann N Y Acad Sci.* 1992; 654:400–15. [PubMed: 1632593]
- O'Brien CP. Anticraving medications for relapse prevention: a possible new class of psychoactive medications. *Am J Psychiatry.* 2005; 162:1423–31. [PubMed: 16055763]
- Oades RD, Halliday GM. Ventral tegmental (A10) system: neurobiology. 1. Anatomy and connectivity. *Brain Res.* 1987; 434:117–165. [PubMed: 3107759]
- Perry CJ, McNally GP. mu-Opioid receptors in the nucleus accumbens shell mediate context-induced reinstatement (renewal) but not primed reinstatement of extinguished alcohol seeking. *Behav. Neurosci.* 2013; 127:535–543. [PubMed: 23895063]
- Peters J, LaLumiere RT, Kalivas PW. Infralimbic prefrontal cortex is responsible for inhibiting cocaine seeking in extinguished rats. *J Neurosci.* 2008; 28:6046–53. [PubMed: 18524910]
- Peters J, Kalivas PW, Quirk GJ. Extinction circuits for fear and addiction overlap in prefrontal cortex. *Learn Mem.* 2009; 16:279–88. [PubMed: 19380710]
- Pickens CL, Airavaara M, Theberge F, Fanous S, Hope BT, Shaham Y. Neurobiology of the incubation of drug craving. *Trends Neurosci.* 2011; 34:411–20. [PubMed: 21764143]
- Pitkanen, A. Connectivity of the rat amygdaloid complex. In: Aggelton, JP., editor. *The amygdala: a functional analysis.* Oxford University Press; Oxford, U.K.: 2000. p. 31-115.
- Rescorla, RA.; Durlach, PJ.; Grau, JW. Contextual learning in Pavlovian conditioning. In: Balsam, P.; Tomie, A., editors. *Context and learning.* Erlbaum; Hillsdale, NJ: 1985. p. 23-56.
- Robins LN, Davis DH, Goodwin DW. Drug use by U.S. Army enlisted men in Vietnam: a followup on their return home. *Am. J. Epidemiol.* 1974; 99:235–49. [PubMed: 4818714]
- Rogers JL, Ghee S, See RE. The neural circuitry underlying reinstatement of heroin-seeking behavior in an animal model of relapse. *Neuroscience.* 2008; 151:579–588. [PubMed: 18061358]
- Rouse ST, Marino MJ, Bradley SR, Awad H, Wittmann M, Conn PJ. Distribution and roles of metabotropic glutamate receptors in the basal ganglia motor circuit: implications for treatment of Parkinson's disease and related disorders. *Pharmacol. Ther.* 2000; 88:427–435. [PubMed: 11337032]
- Schoepp DD. Unveiling the functions of presynaptic metabotropic glutamate receptors in the central nervous system. *J. Pharmacol. Exp. Ther.* 2001; 299:12–20. [PubMed: 11561058]
- Self DW, Barnhart WJ, Lehman DA, Nestler EJ. Opposite modulation of cocaine-seeking behavior by D1- and D2-like dopamine receptor agonists. *Science.* 1996; 271:1586–1589. [PubMed: 8599115]
- Sesack SR, Deutch AY, Roth RH, Bunney BS. Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: An anterograde tract-tracing study with Phaseolus vulgaris leucoagglutinin. *The Journal of Comparative Neurology.* 1989; 290:213–242. [PubMed: 2592611]

- Sesack SR, Carr DB, Omelchenko N, Pinto A. Anatomical substrates for glutamate-dopamine interactions: evidence for specificity of connections and extrasynaptic actions. *Ann. N. Y. Acad. Sci.* 2003; 1003:36–52. [PubMed: 14684434]
- Setlow B, Holland PC, Gallagher M. Disconnection of the basolateral amygdala complex and nucleus accumbens impairs appetitive pavlovian second-order conditioned responses. *Behav. Neurosci.* 2002; 116:267–275. [PubMed: 11996312]
- Shaham Y, Stewart J. Stress reinstates heroin-seeking in drug-free animals: an effect mimicking heroin, not withdrawal. *Psychopharmacology.* 1995; 119:334–341. [PubMed: 7675970]
- Shaham Y, Stewart J. Effects of opioid and dopamine receptor antagonists on relapse induced by stress and re-exposure to heroin in rats. *Psychopharmacology.* 1996; 125:385–391. [PubMed: 8826544]
- Shaham Y, Erb S, Stewart J. Stress-induced relapse to heroin and cocaine seeking in rats: a review. *Brain Res. Brain Res. Rev.* 2000; 33:13–33. [PubMed: 10967352]
- Shalev U, Yap J, Shaham Y. Leptin attenuates acute food deprivation-induced relapse to heroin seeking. *J. Neurosci.* 2001; 21:RC129. [PubMed: 11160414]
- Shalev U, Grimm JW, Shaham Y. Neurobiology of relapse to heroin and cocaine seeking: a review. *Pharmacol. Rev.* 2002; 54:1–42. [PubMed: 11870259]
- Shinonaga Y, Takada M, Mizuno N. Topographic organization of collateral projections from the basolateral amygdaloid nucleus to both the prefrontal cortex and nucleus accumbens in the rat. *Neuroscience.* 1994; 58:389–397. [PubMed: 8152545]
- Sinclair CM, Cleva RM, Hood LE, Olive MF, Gass JT. mGluR5 receptors in the basolateral amygdala and nucleus accumbens regulate cue-induced reinstatement of ethanol-seeking behavior. *Pharmacol. Biochem. Behav.* 2012; 101:329–335. [PubMed: 22296815]
- Sinha R, Shaham Y, Heilig M. Translational and reverse translational research on the role of stress in drug craving and relapse. *Psychopharmacology (Berl).* 2011; 218:69–82. [PubMed: 21494792]
- Spealman RD, Barrett-Larimore RL, Rowlett JK, Platt DM, Khroyan TV. Pharmacological and environmental determinants of relapse to cocaine-seeking behavior. *Pharmacol. Biochem. Behav.* 1999; 64:327–336. [PubMed: 10515309]
- Stankeviciute NM, Scofield MD, Kalivas PW, Gipson CD. Rapid, transient potentiation of dendritic spines in context-induced relapse to cocaine seeking. *Addict Biol.* 2013
- Stewart J. Reinstatement of heroin and cocaine self-administration behavior in the rat by intracerebral application of morphine in the ventral tegmental area. *Pharmacol. Biochem. Behav.* 1984; 20:917–923. [PubMed: 6463075]
- Tiffany ST, Conklin CA. The promise and pitfalls of animal and human models of relapse: comment on Leri and Stewart (2002). *Exp Clin Psychopharmacol.* 2002; 10:361–3. [PubMed: 12498332]
- Urcelay GP, Miller RR. The functions of contexts in associative learning. *Behav. Processes.* 2014; 104:2–12. [PubMed: 24614400]
- Usuda I, Tanaka K, Chiba T. Efferent projections of the nucleus accumbens in the rat with special reference to subdivision of the nucleus: biotinylated dextran amine study. *Brain Res.* 1998; 797:73–93. [PubMed: 9630528]
- Vandergriff J, Rasmussen K. The selective mGlu2/3 receptor agonist LY354740 attenuates morphine-withdrawal-induced activation of locus coeruleus neurons and behavioral signs of morphine withdrawal. *Neuropharmacology.* 1999; 38:217–222. [PubMed: 10218862]
- Weiss F, Maldonado-Vlaar CS, Parsons LH, Kerr TM, Smith DL, Ben-Shahar O. Control of cocaine-seeking behavior by drug-associated stimuli in rats: effects on recovery of extinguished operant-responding and extracellular dopamine levels in amygdala and nucleus accumbens. *Proc. Natl. Acad. Sci. U.S.A.* 2000; 97:4321–4326. [PubMed: 10760299]
- Weiss F, Martin-Fardon R, Ciccocioppo R, Kerr TM, Smith DL, Ben-Shahar O. Enduring resistance to extinction of cocaine-seeking behavior induced by drug-related cues. *Neuropsychopharmacology.* 2001; 25:361–372. [PubMed: 11522464]
- Widholm JJ, Gass JT, Cleva RM, Olive MF. The mGluR5 Positive Allosteric Modulator CDPPB Does Not Alter Extinction or Contextual Reinstatement of Methamphetamine-Seeking Behavior in Rats. *J. Addict. Res. Ther.* 2011; S1:1–12.
- Wikler A. Dynamics of drug dependence. Implications of a conditioning theory for research and treatment. *Arch. Gen. Psychiatry.* 1973; 28:611–616.

- Willcocks AL, McNally GP. The role of medial prefrontal cortex in extinction and reinstatement of alcohol-seeking in rats. *European Journal of Neuroscience*. 2012 n/a-n/a.
- Wing VC, Shoaib M. Contextual stimuli modulate extinction and reinstatement in rodents self-administering intravenous nicotine. *Psychopharmacology*. 2008; 200:357–365. [PubMed: 18587561]
- Wise RA. Opiate reward: sites and substrates. *Neurosci. Biobehav. Rev.* 1989; 13:129–133. [PubMed: 2573023]
- Xie X, Ramirez DR, Lasseter HC, Fuchs RA. Effects of mGluR1 antagonism in the dorsal hippocampus on drug context-induced reinstatement of cocaine-seeking behavior in rats. *Psychopharmacology*. 2010; 208:1–11. [PubMed: 19847405]
- Xie X, Lasseter HC, Ramirez DR, Ponds KL, Wells AM, Fuchs RA. Subregion-specific role of glutamate receptors in the nucleus accumbens on drug context-induced reinstatement of cocaine-seeking behavior in rats. *Addict. Biol.* 2012; 17:287–299. [PubMed: 21521425]
- Xie X, Arguello AA, Wells AM, Reittinger AM, Fuchs RA. Role of a hippocampal SRC-family kinase-mediated glutamatergic mechanism in drug context-induced cocaine seeking. *Neuropsychopharmacology*. 2013; 38:2657–2665. [PubMed: 23872878]
- Xie X, Wells AM, Fuchs RA. Cocaine seeking and taking: role of hippocampal dopamine D1-like receptors. *Int. J. Neuropsychopharmacol.* 2014:1–6. [PubMed: 23953038]
- Yamaguchi T, Sheen W, Morales M. Glutamatergic neurons are present in the rat ventral tegmental area. *Eur. J. Neurosci.* 2007; 25:106–18. [PubMed: 17241272]
- Yamaguchi T, Wang HL, Li X, Ng TH, Morales M. Mesocorticolimbic glutamatergic pathway. *J. Neurosci.* 2011; 31:8476–90. [PubMed: 21653852]

Figure 1.

Schematic illustrating the corticostriatal control of context-induced reinstatement of heroin (A), cocaine (B), and alcohol (C) seeking. Inactivation of brain regions depicted in black decreases context-induced reinstatement of the respective drug. Inactivation of brain regions depicted in gray has no effect on context-induced reinstatement of the respective drug. Brain regions depicted in white have not been tested for involvement in context-induced reinstatement of the respective drug. Red arrows depict projections that are critical for expression of context-induced reinstatement.

Table 1

Effect of intracranial injections of pharmacological agents on context-induced reinstatement of drug seeking. “↓” refers to a decrease in context-induced drug seeking (in the training context where drug was available) due to the manipulation, “—” refers to no effect on context-induced drug seeking due to the manipulation.

	Heroin	Cocaine	Alcohol	References
dmPFC	M+B —	TTX ↓	M+B ↓	(Bossert et al., 2011; Fuchs et al., 2005; Willcocks and McNally, 2012)
vmPFC	M+B ↓	TTX —	M+B —	(Bossert et al., 2011; Fuchs et al., 2005; Willcocks and McNally, 2012)
BLA		TTX ↓	Naloxone-methiodide ↓	(Fuchs et al., 2005; Marinelli et al., 2010)
DHipp		TTX ↓ APS, PP2, or R025-6981 JNJ16259685 ↓ SCH 23390 ↓ M+B ↓ [CA3] M+B — [pDHipp]		(Fuchs et al., 2005; Lasseter et al., 2010; Luo et al., 2011; Xie et al., 2010; Xie et al., 2013; Xie et al., 2014)
NAc Core	LY379268 ↓ SCH 23390 —	M+B ↓ JNJ16259685 or CNQX ↓ Daun02 Inactivation —	SCH 23390 ↓	(Bossert et al., 2006a; Bossert et al., 2007; Chaudhri et al., 2009; Cruz et al., 2014; Fuchs et al., 2008; Xie et al., 2012)
NAc Shell	LY379268 ↓ SCH 23390 ↓	M+B ↓ CNQX ↓ JNJ16259685 — Daun02 Inactivation ↓	SCH 23390 ↓ CART ↓ CTAP ↓	(Bossert et al., 2006a; Bossert et al., 2007; Chaudhri et al., 2009; Cruz et al., 2014; Fuchs et al., 2008; Millan and McNally, 2012; Perry and McNally, 2013; Xie et al., 2012)
dStriatum	LY379268 — SCH 23390 ↓	M+B [dIStr] ↓ CNQX — JNJ16259685 —		(Bossert et al., 2006a; Bossert et al., 2009; Fuchs et al., 2006; Xie et al., 2012)
VTA	LY379268 ↓			(Bossert et al., 2004)
OFC		M+B ↓ [IOFC not mOFC] SCH23390 ↓ [IOFC]		(Lasseter et al., 2009; Lasseter et al., 2014)
VHipp	M+B ↓	M+B ↓		(Bossert and Stern, 2014; Lasseter et al., 2010)
OFC-BLA		Ipsilateral or contralateral M+B ↓ SCH 23390 in OFC and M+B in ipsilateral or contralateral BLA ↓		(Lasseter et al., 2011; Lasseter et al., 2014)
BLA-DHipp		Contralateral M+B ↓		(Fuchs et al., 2007)
BLA-dmPFC		Ipsilateral M+B ↓ Contralateral M+B ↓		(Fuchs et al., 2007)
vmPFC-NAc Shell	M+B in vmPFC and SCH 23390 in contralateral or ipsilateral NAc Shell ↓			(Bossert et al., 2012)
dIStr-NAc Shell	Contralateral SCH 23390 —			(Bossert et al., 2009)
LS-VTA		Contralateral M+B ↓		(Luo et al., 2011)

--Exposure to environmental contexts previously associated with drug use can provoke relapse

--We and others study this clinical condition in rats by using a context-induced reinstatement procedure

--We review results on the role of corticostriatal circuits in context-induced reinstatement of drug seeking