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REVIEW

Role of cues and contexts on drug-seeking behaviour

Christina J Perry[1,2]*, Isabel Zbukvic[1,2]*, Jee Hyun Kim[1,2] and Andrew J Lawrence[1,2]

[1]*Behavioural Neuroscience Division, The Florey Institute of Neuroscience and Mental Health, Parkville, Vic., Australia, and* [2]*Florey Department of Neuroscience and Mental Health, University of Melbourne, Parkville, Vic., Australia*

Correspondence
Dr Christina J Perry, Behavioural Neuroscience Division, The Florey Institute of Neuroscience and Mental Health, Parkville, Vic. 3011, Australia. E-mail: christina.perry@florey.edu.au

*These authors contributed equally to this review.

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Environmental stimuli are powerful mediators of craving and relapse in substance-abuse disorders. This review examined how animal models have been used to investigate the cognitive mechanisms through which cues are able to affect drug-seeking behaviour. We address how animal models can describe the way drug-associated cues come to facilitate the development and persistence of drug taking, as well as how these cues are critical to the tendency to relapse that characterizes substance-abuse disorders. Drug-associated cues acquire properties of conditioned reinforcement, incentive motivation and discriminative control, which allow them to influence drug-seeking behaviour. Using these models, researchers have been able to investigate the pharmacology subserving the behavioural impact of environmental stimuli, some of which we highlight. Subsequently, we examine whether the impact of drug-associated stimuli can be attenuated via a process of extinction, and how this question is addressed in the laboratory. We discuss how preclinical research has been translated into behavioural therapies targeting substance abuse, as well as highlight potential developments to therapies that might produce more enduring changes in behaviour.

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Abbreviations
ACC, anterior cingulate cortex; CET, cue exposure therapy; CPP, conditioned place preference; CS, neutral conditioned stimulus; DCS, D-cycloserine; FR, fixed ratio; MPEP, 2-methyl-6-(phenylethynyl)pyridine; MTEP, 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine; NAc, nucleus accumbens; NAM, negative allosteric modulator; PIT, Pavlovian-to-instrumental transfer; US, unconditioned stimulus

Introduction

The enduring propensity for relapse is one of the cardinal features of substance-abuse disorders (Koob and Le Moal, 1997; O'Brien, 1997). Relapse occurs in response to different precipitating events, including stress and drug priming (Gerber and Stretch, 1975; de Wit and Stewart, 1981; 1983; Shaham and Stewart, 1994; Stewart, 2000). However, one of the strongest triggers for relapse is exposure to environmental stimuli that have become associated with drugs of abuse (Davis and Smith, 1974; See, 2002; 2005). The aim of the current review was to highlight how animal models can be used to elucidate the cognitive and neurobiological mechanisms underpinning how cues and contexts mediate drug-taking and drug-seeking behaviour. In particular, we will focus on how this research can be carried into the clinic.

Cue reactivity and relapse

Environmental cues associated with drugs of abuse are powerful mediators of drug-seeking behaviour. Cues produce

symptoms of withdrawal in humans and laboratory animals, even after full detoxification (Wikler, 1948; Childress *et al.*, 1986; O'Brien *et al.*, 1992). Persons with a history of drug use show enhanced physiological responses to drug-associated cues (cue reactivity) compared with drug-naive counterparts, across many different drug classes (Childress *et al.*, 1986; Drummond, 2000; Foltin and Haney, 2000; Chiamulera, 2005). Self-reported craving for cocaine in response to drug-associated cues correlated with blood flow changes in the amygdala, anterior cingulate cortex (ACC) and basal ganglia in detoxified cocaine users compared with naive counterparts, suggesting that drug use has changed the way these cues are processed (Childress *et al.*, 1999). Importantly, cue reactivity and cue-induced craving predict, to some degree, relapse in alcoholics (Niaura *et al.*, 1988; Rohsenow *et al.*, 1994; Cooney *et al.*, 1997; Grusser *et al.*, 2004), smokers (Niaura *et al.*, 1988) and cocaine users (Back *et al.*, 2010). These observations highlight the importance of investigating psychological and pharmacological mechanisms underlying cue-mediated drug-seeking behaviour. If drug-associated cues predict relapse, then it is critical that we understand how they come to possess such behaviourally salient properties.

Environmental stimuli impact drug-seeking behaviour via a process of associative learning

Learning and memory processes play a critical role in the development and maintenance of drug-seeking behaviour. Broadly, there are two behavioural modification processes that occur with repeated drug use. The drug user learns first that there is an action–outcome relationship between drug-taking activities and the rewarding experience. This type of learning is referred to as instrumental conditioning, and occurs when an operant response incurs a particular outcome. The positive outcome consequently increases the tendency for the response to reoccur (i.e. it acts as a reinforcer) (Thorndike, 1898; Skinner, 1948; 1958; Morse and Skinner, 1958). With repeated drug experience, the drug user associates the rewarding effects of a drug with cues present at the time of drug taking. This is classical, or Pavlovian, conditioning, which refers to the association formed between a neutral conditioned stimulus (CS) and a biologically relevant unconditioned stimulus (US) (Pavlov, 1927). There is a clear distinction between these two forms of learning; unlike instrumental conditioning, Pavlovian conditioning is a passive process whereby the occurrence of either the US or the CS is not necessarily dependent on the behaviour of the animal (Rescorla and Soloman, 1967). However, Pavlovian associations can function as powerful mediators of instrumentally conditioned behaviours (Baker *et al.*, 1991). Critically, in the case of drug addiction, it is through these Pavlovian associations that innocuous environmental stimuli become salient mediators of drug-seeking behaviour.

Animal models can elucidate how cues mediate drug-seeking behaviour

Like humans, animals will readily self-administer drugs of abuse (Weeks, 1962). The drug self-administration procedure allows researchers to investigate analogues of the major elements of human drug addiction: acquisition, inhibition and reinstatement (or 'relapse') of drug seeking. The self-administration model has been reviewed extensively elsewhere (e.g. Shaham *et al.*, 2003; Spanagel, 2003; Bossert *et al.*, 2013), and is widely regarded as one of the best animal models to study drug abuse because of its strong face and construct validity (Feltenstein and See, 2009). In this model, animals are trained to perform a specific operant conditioned response such as a lever press or nose poke in order to obtain drug reinforcement. By increasing the number of responses required to earn a drug reward on a fixed or progressive ratio, the motivational value of a range of drugs can be determined (Richardson and Roberts, 1996). Once self-administration is stable, animals can be trained to inhibit drug-seeking behaviour by the process of extinction (Pavlov, 1927). Alternatively, removing animals from drug-conditioning apparatus without providing extinction training provides a model of abstinence, and produces what is known as incubation of craving (Grimm *et al.*, 2001). This is also known as withdrawal. Following extinction or withdrawal, or a combination of the two, relapse can be modelled by the ability of a various precipitators to reinstate conditioned drug seeking (Shalev *et al.*, 2002). Importantly, triggers of reinstatement in animals, such as stress, drug-priming or drug-associated cues, are likewise known to contribute to relapse in human drug-abusers (Shalev *et al.*, 2002; Lee *et al.*, 2006). The neurobiology underlying reinstatement is complex, and a comprehensive review is beyond the scope of this paper. However, a summary of the available literature on acute, systemic pharmacological manipulations given prior to reinstatement reveals that a range of neurotransmitter and neuropeptide systems are differentially involved in this behaviour, depending on the drug of abuse and the precipitating factor. This can be clearly seen in Tables 1–5, which show the effects of systemic, i.c.v. or oral administration of pharmacological agents on cue-, stress- and drug-primed reinstatement of drug-seeking behaviour after extinction. In this summary, cue refers to a discrete cue, or a discrete cue in combination with a discriminative cue, and not to reinstatement precipitated by discriminative cues alone. It is worth noting that in all of the studies shown, the treatments were delivered acutely, prior to reinstatement session. In addition, all reinstatement sessions took place in the absence of further primary reinforcement, with the exception of the study by Justinova *et al.* (2010) examining reinstatement of cannabinoid seeking, which was included as literature on this drug class is so scarce. Findings are reported for male animals only.

Importantly, in addition to motivation for drug itself, variants of the self-administration model allow for the study of drug-associated cues in drug taking, extinction and in reinstatement (Figure 1). When drug delivery is paired with the activation of a cue such as a light or a tone, this stimulus becomes a CS to the drug (Davis and Smith, 1974). This is termed a discrete cue, also referred to as a CS throughout the present review. On the other hand, a cue can also act as an indicator of drug availability or unavailability. In such a procedure, an animal is trained to lever press/nose poke for drug or a neutral reinforcer in two distinct conditions. In one of these conditions a particular odour (the S+) is present in the chamber. Drug delivery then occurs in conjunction with a

Table 1

Psychostimulant-seeking behaviour: effect of pharmacological agents on cue-, stress- and drug-primed reinstatement

System	Reference	Cue	Stress	Prime
Adenosine				
A_1 adenosine receptor agonist				
N6-cyclopentyladenosine (CPA)	Hobson *et al.*, 2013			Decreased
Adrenoceptors				
α_1 adrenoceptor antagonist				
Prazosin	Zhang *et al.*, 2005			Decreased
α_2 adrenoceptor agonist				
Clonidine	Erb *et al.*, 2000		Decreased	No effect
	Platt *et al.*, 2007			Decreased
	Lee *et al.*, 2003		Decreased	
Lofexidine	Erb *et al.*, 2000		Decreased	No effect
Guanabenz	Erb *et al.*, 2000		Decreased	No effect
Noradrenaline transport inhibitor				
Nisoxetine	Platt *et al.*, 2007			Increased
Talsupram	Platt *et al.*, 2007			Increased
Dopamine β-hydroxylase inhibitor				
Nepicast	Schroeder *et al.*, 2013	Decreased	Decreased	
	Schroeder *et al.*, 2010			Decreased
Cannabinoid receptors				
CB_1 receptor antagonist				
SR141716A (Rimonabant)	De Vries *et al.*, 2001	Decreased	No effect	Decreased
	Filip *et al.*, 2006	Decreased		Decreased
	Ward *et al.*, 2009	Decreased		
	Anggadiredja *et al.*, 2004	Decreased		Decreased
AM251	Xi *et al.*, 2006			Decreased
	Boctor *et al.*, 2007			No effect
	Schindler *et al.*, 2010	Decreased*		Decreased*
	Adamczyk *et al.*, 2012	Decreased		Decreased
CB_2 receptor antagonist				
SR144528	Adamczyk *et al.*, 2012	No effect		Decreased
TRPV1 receptor antagonist				
SB366791	Adamczyk *et al.*, 2012	No effect		Decreased
Fatty-acid-amide-hydrolase (FAAH) inhibitor				
PMSF	Adamczyk *et al.*, 2009	Decreased		Decreased
URB597	Adamczyk *et al.*, 2009	Decreased		Decreased
Mixed cannabinoid receptor agonist				
Δ^9-tetrahydrocannabinol (THC)	Anggadiredja *et al.*, 2004	Increased		Decreased
Corticosterone				
Corticosterone synthesis inhibitor				
Ketoconazole	Mantsch *et al.*, 1999a			No effect
	Mantsch *et al.*, 1999b		Decreased	
	Moffett *et al.*, 2006	No effect		No effect
	Goeders and Clampitt, 2002	Decreased		
Metyrapone	Nawata *et al.*, 2012		No effect	

Table 1

Continued

System	Reference	Cue	Stress	Prime
Dopamine				
D_1 receptor agonist				
SKF-38393	Alleweireldt *et al.*, 2001	No effect		
	Khroyan *et al.*, 2000	Decreased*		Decreased*
SKF-83959	Khroyan *et al.*, 2000	Decreased*		Decreased*
SKF-81297	Alleweireldt *et al.*, 2001	Decreased		
	Khroyan *et al.*, 2000	Decreased*		Decreased*
SKF-81958	Khroyan *et al.*, 2000	Decreased*		Decreased*
D_1 receptor antagonist				
SCH-23390	Alleweireldt *et al.*, 2001	Decreased		
	Schenk *et al.*, 2011			Decreased
Ecopipam	Khroyan *et al.*, 2000	Decreased*		Decreased*
D_2 receptor agonist				
NPA, *R*(–)-propylnorapomorphine hydrochloride	Khroyan *et al.*, 2000	No effect*		No effect*
PD-128,907	Khroyan *et al.*, 2000	No effect*		No effect*
Terguride	Khroyan *et al.*, 2000	Decreased*		Decreased*
SDZ-208-911	Khroyan *et al.*, 2000	Decreased*		Decreased*
D_2 receptor partial agonist				
Aripiprazole	Feltenstein *et al.*, 2007	Decreased		Decreased
D_2 receptor antagonist				
Eticlopride	Khroyan *et al.*, 2000	Decreased*		Decreased*
	Schenk *et al.*, 2011			Decreased
Nemonapride	Khroyan *et al.*, 2000	Decreased*		Decreased*
Raclopride	Cervo *et al.*, 2003++	Decreased		
D_3 receptor agonist				
7-OH-DPAT	Khroyan *et al.*, 2000	No effect*		No effect*
	Cervo *et al.*, 2003++	Decreased		
D_3 receptor antagonist				
NGB 2904	Xi *et al.*, 2005			Decreased
	Gilbert *et al.*, 2005	Decreased		
	Xi *et al.*, 2007	Decrease		Decreased
SB-277011A	Xi *et al.*, 2004		Decreased	
	Gilbert *et al.*, 2005	Decreased		
	Cervo *et al.*, 2007++	Decreased		
S33138	Peng *et al.*, 2009			Decreased
SR 21502	Galaj *et al.*, 2013	Decreased		
D_4/D_3 receptor antagonist				
YM-43611	Khroyan *et al.*, 2000	Decreased*		Decreased*
AJ-76	Khroyan *et al.*, 2000	No effect*		No effect*
UH 232	Khroyan *et al.*, 2000	No effect*		No effect*
Mixed D_3 agonist/antagonist				
BP-897	Gilbert *et al.*, 2005	Decreased		
Non-selective antagonist				
Flupenthixol	Khroyan *et al.*, 2000	Decreased*		Decreased*
	Platt *et al.*, 2007			Decreased
	Lee *et al.*, 2003		No effect	

Table 1

Continued

System	Reference	Cue	Stress	Prime
Levo-tetrahydropalmatine (*l*-THP)	Figueroa-Guzman *et al.*, 2011	Decreased	Decreased	Decreased
	Mantsch *et al.*, 2007			Decreased
Indirect dopamine modulator				
Modafinil	Mahler *et al.*, 2012a			Decreased
GABA				
$GABA_A$ receptor PAM				
Allopregnanolone	Anker *et al.*, 2010		No effect	
$GABA_B$ receptor agonist				
Baclofen	Filip and Frankowska, 2007	Decreased		Decreased
	Weerts *et al.*, 2007			Decreased
CGP44532	Weerts *et al.*, 2007			Decreased
SKF 97541	Filip and Frankowska, 2007	Decreased		Decreased
$GABA_B$ receptor antagonist				
SCH 50911	Filip and Frankowska, 2007	Decreased		Decreased
GABA reuptake inhibitor				
Tiagabine	Weerts *et al.*, 2007			No effect
$GABA_B$ receptor positive allosteric modulator				
CGP 7930	Filip and Frankowska, 2007	Decreased		Decreased
Glutamate				
AMPA/kainate antagonist				
CNQX	Bäckström and Hyytiä, 2005a,b	Decreased		
NBQX	Bäckström and Hyytiä, 2005a,b	Decreased		
AMPA antagonist				
GYKI 52466	Srivastava *et al.*, 2012			No effect
NMDA/glycine antagonist				
L-701,324	Bäckström and Hyytiä, 2005a,b	Decreased		
NMDA antagonist				
CGP-39551	Bäckström and Hyytiä, 2005a,b	No effect		
D-CPPene	Bespalov *et al.*, 2000	Decreased		No effect
MK-801 (Dizocilpine)	Lee *et al.*, 2005a			No effect
NMDA channel blocker				
Memantine	Bespalov *et al.*, 2000	No effect		No effect
$mGlu_{2/3}$ receptor agonist				
LY379268	Adewale *et al.*, 2006	Decreased*		Decreased*
	Peters and Kalivas, 2006			Decreased
	Baptista *et al.*, 2004++	Decreased		
	Martin-Fardon and Weiss, 2011		Decreased	
	Kufahl *et al.*, 2013	Decreased		Decreased
$mGlu_{2/3}$ receptor antagonist				
LY341497	Li *et al.*, 2010			No effect
$mGlu_5$ positive allosteric modulator				
CDPPB	Moussawi, *et al.*, 2009			No effect
$mGlu_5$ negative allosteric modulator				
MTEP	Kumaresan *et al.*, 2009	Decreased		Decreased
	Gass *et al.*, 2008	Decreased		Decreased
	Iso, *et al.*, 2006	Decreased		

Table 1

Continued

System	Reference	Cue	Stress	Prime
	Martin-Fardon and Weiss., 2011		Decreased	
MPEP	Bäckström and Hyytiä, 2005a,b	Decreased		
	Lee *et al.* 2005a			Decreased
	Kumarasen *et al.*, 2009			Decreased
	Moussawi, *et al.*, 2009			Decreased
	Iso *et al.*, 2006	No effect		
Fenobam sulfate	Keck *et al.*, 2013			Decreased
	Watterson *et al.*, 2012	Decreased		Decreased
$mGlu_7$ positive allosteric modulator				
AMN082	Li *et al.*, 2010			Decreased
N-acetylated-α-linked- acidic dipeptidase inhibitor				
2-PMPA	Xi *et al.*, 2010			Decreased
Indirect glutamate modulator				
N-acetylcysteine	Baker *et al.*, 2003a			Decreased
L-2-oxothiazolidine-4-carboxilic acid	Baker *et al.*, 2003b			Decreased
	Kau *et al.*, 2008			Decreased
Neuropeptides				
Corticotropin-releasing factor (CRF)				
CRF_1 receptor antagonist				
CP-154,526	Shaham *et al.*, 1998		Decreased	
	Moffett *et al.*, 2006	No effect		Decreased
	Goeders and Clampitt, 2002	Decreased		
NB127914	Nawata *et al.*, 2012		Decreased	
$CRF_{1/2}$ receptor antagonist				
D-Phe CRF	Erb *et al.*, 1998		Decreased	No effect
Non-selective CRF antagonist				
α-Helical CRF 9-14	Nawata *et al.*, 2012		Decreased	
Neuropeptide S (NPS)				
NPS	Kallupi *et al.*, 2010++	Increased		
NPS receptor antagonist				
RTI-118	Schmoutz *et al.*, 2012	Decreased	Decreased	Decreased
NPSR-QA1	Kallupi *et al.*, 2012++	Decreased		
SHA 68	Kallupi *et al.*, 2010++	Decreased		
Neurotensin				
Neurotensin receptor antagonist				
SR142948	Torregrossa and Kalivas, 2008			Decreased
Melanin-concentrating hormone (MCH)				
MCH_1 receptor selective antagonist				
TPI 1361-17	Chung *et al.*, 2009	Decreased	No effect	Decreased
NK_1 receptor antagonist				
L822429	Schank *et al.*, 2013		Decreased	
	Zhou *et al.*, 2012	Decreased	Decreased	No effect
	Zhou *et al.*, 2012	Decreased*	Decreased**	Decreased*
	Mahler *et al.*, 2012b			No effect
	Kallupi *et al.*, 2010++	No effect		
	Smith *et al.*, 2007	Decreased		No effect

Table 1

Continued

System	Reference	Cue	Stress	Prime
Opioid receptors				
κ-Opioid receptor agonist				
Enadoline	Rüedi-Bettschen *et al.*, 2009			Decreased
Spiradoline	Rüedi-Bettschen *et al.*, 2009			Decreased
κ-Opioid receptor antagonist				
JDTic	Beardsley *et al.*, 2005		Decreased	
Mixed opioid receptor antagonist				
Naltrexone	Burattini *et al.*, 2007++	Decreased		
	Häggkvist *et al.*, 2009			Decreased
Opioid receptor-like1 endogenous ligand				
Nociceptin/orphanin FQ	Martin-Fardon *et al.*, 2000		No effect	
Orexin				
OX_1 receptor antagonist				
SB-334867	Boutrel *et al.*, 2005		Decreased	
OX_2 receptor antagonist				
4PT	Smith *et al.*, 2009	No effect		
Substance P				
NK_1 receptor antagonist				
RP67580	Placenza *et al.*, 2005			No effect
GR82334	Placenza *et al.*, 2005			No effect
Nicotinic ACh receptor				
Nicotinic ACh receptor agonist				
Nicotine	Hiranita *et al.*, 2006	Decreased		Decreased
AChE inhibitor				
Donepezil	Hiranita *et al.*, 2006	Decreased		Decreased
Opioid receptor-like 1 receptor (NOP) ligand				
Nociceptin (N/OFQ)	Martin-Fardon *et al.*, 2000		No effect	
Serotonin				
5-HT_{1A} receptor agonist				
WAY 100635	Burmeister *et al.*, 2004	No effect		Decreased
	Cervo *et al.*, 2003++	No effect		
Busiprone	Shelton *et al.*, 2013	Decreased		Decreased
5-$HT_{1B/1A}$ receptor agonist				
RU24969	Acosta *et al.*, 2005	Decreased		Decreased
5-HT_{1B} receptor agonist				
CP 94253	Przegaliński *et al.*, 2008	Decreased		Decreased
	Miszkiel and Przegaliński, 2013	No effect*		Decreased
5-HT_{1B} receptor antagonist				
SB 216641	Przegaliński *et al.*, 2008	Decreased		Decreased
	Miszkiel and Przegaliński, 2013	Decreased*		Decreased
GR 127935	Przegaliński *et al.*, 2008	Decreased		Decreased
5-$HT_{2A/C}$ receptor agonist				
Ketanserin	Burmeister *et al.*, 2004	Decreased		No effect
5-HT_{2A} receptor antagonist				
M100,907	Fletcher *et al.*, 2002			Decreased
	Nic Dhonnchadha *et al.*, 2009	Decreased		

Table 1

Continued

System	Reference	Cue	Stress	Prime
SR 46349B	Filip, 2005	Decreased		Decreased
5-$HT_{2C/2B}$ receptor agonist				
MK 212	Neisewander and Acosta, 2007	Decreased		Decreased
Ro 60-0175	Burbassi and Cervo, 2007++	Decreased		
5-HT_{2C} receptor agonist				
Ro 60-0175	Grottick *et al.*, 2000			Decreased
	Fletcher *et al.*, 2007		Decreased	
	Manvich *et al.*, 2012	Decreased*		Decreased*
SB 242,084	Burmeister *et al.*, 2004	No effect		No effect
	Fletcher *et al.*, 2002			Increased
	Burbassi and Cervo, 2007++	No effect		
WAY 163909	Cunningham *et al.*, 2011	Decreased		
m-chlorophenylpiperazine (mCPP)	Manvich *et al.*, 2012	Decreased*		Decreased*
5-HT_{2C} receptor antagonist				
SDZ SER-082	Filip, 2005	No effect		No effect
5-HT reuptake inhibitor				
Citalopram	Rüedi-Bettschen *et al.*, 2009			Decreased
	Howell and Negus, 2014			Decreased
Fluoxetine	Rüedi-Bettschen *et al.*, 2009			Decreased
	Burmeister *et al.*, 2003a,b	Decreased		No effect
	Howell and Negus, 2014			Decreased
	McClung *et al.*, 2010			Decreased
d-fenfluramine	Burmeister *et al.*, 2003a,b	Decreased		No effect
Clomipramine	Schenk *et al.*, 2011	Decreased		
Other manipulations (mixed actions)				
Aldehyde dehydrogenase-2 inhibitor (ALDH2i)	Yao *et al.*, 2010	Decreased		Decreased
Diclofenac	Anggadiredja *et al.*, 2004	Decreased		Decreased
Disulfram (Antabuse)	Schroeder *et al.*, 2010			Decreased
Galantamine	Koseki *et al.*, 2012	Decreased		
1MeTIQ	Antkiewicz-Michaluk *et al.*, 2007			Decreased
Mirtazapine (Remeron)	Graves *et al.*, 2011	Decreased		

Key: *, CS/prime; **, stress/CS; ++, S+/CS+.

particular discrete cue (the CS+). In the second condition, an alternate odour (the S–) signals that lever presses will result in water or saline, delivered in conjunction with a different CS (the CS–). Using this type of protocol, during conditioning, responding is higher in the S+/CS+ condition that in the S–/CS– condition (Ciccocioppo *et al.*, 2002; 2003; Burattini *et al.*, 2008). The combined S and CS are referred to as a discriminative cue (Estes, 1948). Using the self-administration procedure, it is also possible to examine the role of cues in extinction. Firstly, instrumental responding can be extinguished in the presence or the absence of the discrete or discriminative drug-associated cue. Secondly, the discrete or discriminative cue itself can be extinguished separately from the instrumental response. Thirdly, cues or instrumental responding can be extinguished in a different context to the self-administration context, distinguished by factors such as floor or wall texture, odour, and chamber size or shape. These are referred to as contextual cues. Finally, reinstatement can be precipitated by re-exposure to discrete cues, discriminative cues or contextual cues that were associated with self-administration, the latter of which is referred to as renewal. Overall, the self-administration model can be employed in various ways to provide a great deal of information about the role of cues in drug-seeking behaviour.

The pharmacology involved in cue-mediated drug-seeking behaviour shares many common mechanisms with normal learning processes (e.g. Koob, 2009; Olive, 2010). In particular, the metabotropic glutamate 5 (mGlu5) receptor is known to play an important role in learning and memory (Kelley, 2004; Malenka and Bear, 2004; Hyman *et al.*, 2006; receptor

Table 2

Alcohol-seeking behaviour: effect of pharmacological agents on cue-, stress- and drug-primed reinstatement

System	Reference	Cue	Stress	Prime
Adrenoceptors				
α_1 receptor antagonist				
Prazosin	Lê *et al.*, 2011		Decreased	
α_2 receptor agonist				
Clonidine	Lê *et al.*, 2009		Decreased	
Guanfacine	Lê *et al.*, 2011		Decreased	
Lofexidine	Lê *et al.*, 2005		Decreased	
Cannabinoid receptors				
CB_1 receptor antagonist				
SR141716A	Cippitelli *et al.*, 2005#	Decreased		
	Economidou *et al.* (2005)#	Decreased		
Endocannabinoid (anandamide) uptake inhibitor				
AM404	Cippitelli *et al.*, 2007++	No effect		
Fatty acid amide hydrolase (FAAH) inhibitor				
URB597	Cippitelli *et al.*, 2008++	No effect	No effect	
Dopamine				
D_3 receptor antagonist				
SB-277011-A	Vorel *et al.*, 2002			Decreased
	Vengeliene *et al.*, 2006	Decreased		
	Heidbreder *et al.*, 2007	Decreased*		Decreased*
BP 897	Vengeliene *et al.*, 2006	Decreased		
Glutamate				
AMPA receptor antagonist				
GYKI 52466	Sanchis-Segura *et al.*, 2006	Decreased		
AMPA positive allosteric modulator				
Aniracetam	Cannady *et al.*, 2012	Increased		
AMPA/kainate receptor antagonist				
CNQX	Bäckström and Hyytiä, 2004	Decreased*		Decreased*
NMDA receptor antagonist				
CGP39551	Bäckström and Hyytiä, 2004	No effect*		No effect*
MK-801	Bäckström and Hyytiä, 2004	No effect*		No effect*
Neramexane	Bachteler *et al.*, 2005++	No effect		
NMDA/glycine receptor antagonist				
L-701,324	Bäckström and Hyytiä, 2004	Decreased*		Decreased*
$mGlu_{2/3}$ receptor agonist				
LY379268	Zhao *et al.*, 2006		Decreased	
	Bäckström and Hyytiä, 2005a,b++	Decreased*		Decreased*
	Sidhpura *et al.*, 2010		Decreased	
$mGlu_5$ negative allosteric modulator				
MPEP	Bäckström *et al.*, 2004++	Decreased*		Decreased*
	Schroeder, *et al.*, 2008	Decreased		
MTEP	Sidhpura *et al.*, 2010		Decreased	
$mGlu_8$ receptor agonist				
(S)-3.4-DCPG	Bäckström and Hyytiä, 2005a,b	Decreased*		Decreased*

Table 2

Continued

System	Reference	Cue	Stress	Prime
Glucocorticoid receptor				
Glucocorticoid receptor antagonist				
RU-486 (Mifepristone)	Simms *et al.*, 2011		Decreased	
Neuropeptides				
Corticotropin-releasing factor (CRF)				
CRF receptor antagonist				
Antalarmin	Marinelli *et al.*, 2007		Decreased	
	Hansson *et al.*, 2006		Decreased	
CP-154,526	Lê *et al.*, 2000		Decreased	
D-Phe-CRF	Lê *et al.*, 2000		Decreased	
	Liu and Weiss, 2002	No effect	Decreased	
MTIP	Gehlert *et al.*, 2007		Decreased	
Melanin concentrating hormone (MCH)				
MCH receptor antagonist				
GW803430	Cippitelli *et al.*, 2010		Decreased	
NK_1 receptor				
NK_1 receptor antagonist				
L822429	Schank *et al.*, 2011		Decreased	No effect
Neuropeptide S (NPS)				
NPS	Cannella *et al.*, 2009++	Increased		
Neuropeptide Y (NPY)				
NPY	Cippitelli *et al.*, 2009		Decreased	
NPY Y_2 receptor antagonist				
JNJ-31020028	Cippitelli *et al.*, 2011		No effect	
Opioid receptors				
δ-Opioid receptor antagonist	Ciccocioppo *et al.*, 2002++	Decreased		
Naltrindole				
δ-Opioid receptor antagonist/μ-opioid receptor agonist	Nielsen *et al.*, 2011		Decreased***	
SoRI-9409				
κ-Opioid receptor antagonist	Schank *et al.*, 2012	Decreased	No effect	
JDTic				
μ-Opioid receptor antagonist	Ciccocioppo *et al.*, 2002++	Decreased		
Naloxonazine				
Opioid receptor antagonist				
Naltrexone	Lê *et al.*, 1999		No effect	Decreased
	Liu *et al.*, 2002	Decreased		
	Liu and Weiss, 2002	Decreased	No effect	
	Ciccocioppo *et al.*, 2002++	Decreased		
	Heidbreder *et al.*, 2007	No effect*		No effect*
	Williams and Schimmel, 2008	Decreased		
Opioid receptor-like 1 receptor (NOP) ligand				
Nociceptin (N/OFQ)	Ciccocioppo *et al.*, 2004++	Decreased		
	Martin-Fardon *et al.*, 2000		Decreased	
Orexin				
OX_1 receptor antagonist				
SB-334867	Jupp, *et al.*, 2011	Decreased		

Table 2

Continued

System	Reference	Cue	Stress	Prime
	Richards *et al.*, 2008		Decreased	
	Cannella *et al.*, 2009++	No effect		
	Lawrence *et al.*, 2006	Decreased		
OX_2 receptor antagonist				
TCS-OX2-29	Brown *et al.*, 2013	No effect		
Relaxin-3				
RXFP3 receptor antagonist				
R3B(1-22)R	Ryan *et al.*, 2013++	Decreased	Decreased	
R3(BD23–27)R/I5	Ryan *et al.*, 2013++	Decreased		
Nicotinic receptor				
Nicotinic mixed partial agonist				
Varenicline (Champix)	Wouda *et al.*, 2011	Decreased		
	Le Foll *et al.*, 2011	Decreased		
Serotonin				
$5HT_{1A}$ receptor antagonist				
WAY 100,635	Lê *et al.*, 2009		Decreased	
5-HT_3 receptor antagonist				
Ondansetron	Lê *et al.*, 2006		Decreased	
Tropisetron	Lê *et al.*, 2006		Decreased	
5-HT_6 receptor antagonist				
CPM 42	de Bruin *et al.*, 2013	Decreased*		Decreased*
5-HT reuptake inhibitor	Lê *et al.*, 2006		Decreased	
Dexfenfluramine				
Fluoxetine (Prozac)	Lê *et al.*, 1999		Decreased	No effect
Other manipulations (mixed actions)				
Acamprosate	Heidbreder *et al.*, 2007	No effect*		No effect*
	Spanagel *et al.*, 2014++	No effect		
	Bachteler *et al.*, 2005++	Decreasd		
BD1047	Martin-Fardon *et al.*, 2012++	Decreased		
Calcium	Spanagel *et al.*, 2014++	Decreased		
CVT-10216	Arolfo *et al.*, 2009	Decreased		
Lamotrigine	Vengeliene *et al.*, 2007++	Decreased		
NO gas	Vengeliene *et al.*, 2014++	No effect		
Pioglitazone	Stopponi *et al.*, 2011	No effect	Decreased	
Xenon gas	Vengeliene *et al.*, 2014++	Decreased		

Key: *, CS/prime; ***, stress/prime; ++, S+/CS+; #, S+/CS+/prime.

nomenclature follows Alexander *et al.*, 2013). mGlu5 receptors belong to the class of group 1 metabotropic glutamate receptors, and are linked via scaffold proteins including Shank and Homer to the NMDA receptor (Bird and Lawrence, 2009; Niswender and Conn, 2010; Duncan and Lawrence, 2012). Through this mechanism, they are implicated in regulation of the induction and maintenance of synaptic plasticity, the putative neurochemical basis of learning and memory (Olive, 2010). Critically, mGlu5 receptors are distributed throughout the neural circuitry involved in reward-driven behaviours (Shigemoto *et al.*, 1993; Romano *et al.*, 1995). For these reasons, the mGlu5 receptor has received considerable attention in recent years as a potential therapeutic target for the treatment of drug addiction (Bird and Lawrence, 2009; Olive, 2010; Duncan and Lawrence, 2012; Myers *et al.*, 2011). The current review will focus on evidence for the role of the mGlu5 receptor in the development and persistence of drug-seeking behaviours specifically mediated by drug-associated cues.

Table 3

Nicotine-seeking behaviour: effect of pharmacological agents on cue-, stress- and drug-primed reinstatement

System	Reference	Cue	Stress	Prime
Adrenoceptors				
α_2 adrenoceptor agonist				
Clonidine	Zislis *et al.*, 2007		Decreased	
β-adrenoceptor antagonist				
Propranolol	Chiamulera *et al.*, 2010	Decreased		
Noradrenaline α_1 adrenoceptor antagonist				
Prazosin	Forget *et al.*, 2010	Decreased		Decreased
ACh				
ACh receptor positive allosteric modulator				
Galantamine	Hopkins *et al.*, 2012			Decreased
Peroxisome proliferator-activated receptor-α (PPARα)				
PPARα agonist				
Clofibrate	Panlilio *et al.*, 2012	Decreased		Decreased
methOEA	Mascia *et al.*, 2011	Decreased*		Decreased*
WY14643	Mascia *et al.*, 2011	Decreased*		Decreased*
Cannabinoid receptors				
CB_1 receptor antagonist				
SR141716A (Rimonabant)	De Vries *et al.*, 2005	Decreased		
	Forget *et al.*, 2009	Decreased		Decreased
	Cohen *et al.*, 2004	Decreased		
AM251	Shoaib, 2008	Decreased*		Decreased*
$CB_{1/2}$ receptor agonist				
WIN 55,212-2	Gamaleddin *et al.*, 2011b	Increased		
CB_2 receptor antagonist				
AM630	Gamaleddin *et al.*, 2012	No effect		No effect
CB_2 receptor agonist				
AM1241	Gamaleddin *et al.*, 2012	No effect		No effect
Endocannabinoid (anandamide) uptake inhibitor				
VDM11	Gamaleddin *et al.*, 2011a	Decreased		Decreased
AM404	Gamaleddin *et al.*, 2013	Decreased		Decreased
Fatty acid amide hydrolase (FAAH) inhibitor				
URB597	Forget *et al.*, 2009	No effect		No effect
	Scherma *et al.*, 2008			Decreased
Dopamine				
D_1 receptor antagonist				
SCH23390	Cohen *et al.*, 2004	Decreased		
	Liu *et al.*, 2010	Decreased		
D_2 receptor agonist				
Bifeprunox	Di Clemente *et al.*, 2011++	Decreased		
D_2 receptor antagonist				
Eticlopride	Liu *et al.*, 2010	Decreased		
D_3 receptor agonist				
BP 897	Khaled *et al.*, 2009	No effect		
D_3 receptor antagonist				
SB 277011-A	Khaled *et al.*, 2009	Decreased		

Table 3

Continued

System	Reference	Cue	Stress	Prime
D_4 receptor antagonist				
L-745,870	Yan *et al.*, 2011	Decreased		Decreased
GABA				
$GABA_B$ receptor agonist				
Baclofen	Fattore *et al.*, 2009			Decreased
CGP44532	Paterson *et al.*, 2005	Decreased		
$GABA_B$ receptor positive allosteric modulator				
BHF177	Vlachou *et al.*, 2009	Decreased		
	Vlachou *et al.*, 2011	Decreased		
Glutamate				
$mGlu_1$ antagonist				
EMQMCM	Dravolina *et al.*, 2007	Decreased		Decreased
$mGlu_{2/3}$ receptor agonist				
LY379268	Liechti *et al.*, 2007	Decreased		
$mGlu_5$ negative allosteric modulator				
MPEP	Bespalov *et al.*, 2005	Decreased		
Glycine transport inhibitor				
SSr504734	Cervo *et al.*, 2013++			
Indirect glutamate modulator				
N-acetylcysteine	Ramirez-Niño *et al.*, 2012	Decreased		
Neuropeptides				
Corticotropin-releasing factor (CRF)				
$CRF_{1/2}$ receptor antagonist				
D-Phe CRF (12-41)	Zislis *et al.*, 2007		Decreased	
CRF_1 receptor antagonist				
R278995/CRA0450	Bruijnzeel *et al.*, 2009		Decreased	
Antalarmin	Plaza-Zabala *et al.*, 2010		Decreased	
CRF_2 receptor antagonist				
Astressin-2B	Bruijnzeel *et al.*, 2009		No effect	
Opioids				
Opioid receptor antagonist				
Naltrexone	Liu *et al.*, 2009	Decreased		
Orexin				
OX_1 receptor antagonist				
SB334867	Plaza-Zabala *et al.*, 2010		No effect	
Nicotinic receptor				
Nicotinic ACh receptor antagonist				
α4β2-selective antagonist dihydro-β-erythroidine (DHβE)	Liu, 2013	No effect		
α7-selective antagonist methyllycaconitine (MLA)	Liu, 2013	Decreased		
Mecamylamine	Liu *et al.*, 2006	Decreased		
Mixed partial cholinergic receptor agonist				
Varenicline	O'Connor *et al.*, 2010b	No effect		Decreased
	Wouda *et al.*, 2011	Increased		
Serotonin				
$5\text{-}HT_{2C}$ receptor agonist				
Lorcaserin	Higgins *et al.*, 2011	Decreased*		Decreased*

Table 3

Continued

System	Reference	Cue	Stress	Prime
Ro60-0175	Fletcher *et al.*, 2012	Decreased		Decreased
5-HT_{2C} receptor antagonist				
M100907 (Volinanserin)	Fletcher *et al.*, 2012	Decreased		Decreased
5-HT_6 receptor antagonist				
CPM 42	de Bruin *et al.*, 2013	Decreased*		Decreased*
Other manipulations (mixed actions)				
Buproprion	Liu *et al.*, 2007	Increased		
	Dwoskin *et al.*, 2006			Decreased

Key: *, CS/prime; ++, S+/CS+.

Role of cues in drug intake

Discrete cues enhance drug intake. Drug experiences are inevitably associated with cues in the environment, and animal studies show that when presented contiguously with drug delivery, a discrete cue can actually enhance intake of drug. This has been shown most consistently with nicotine. For example, acquisition of a response reinforced with nicotine was more rapid and more persistent under increasing fixed ratio (FR) schedule demands when nicotine infusions were paired with a compound visual cue (Caggiula *et al.*, 2002). Rats responding for nicotine together with this cue increased the number of responses made, resulting in stable levels of drug intake despite the increased workload. Conversely, rats responding for nicotine without any visual cue decreased their response rates to near extinction levels as demands increased to an FR 5 schedule. Rates of reacquisition after extinction were also much greater when nicotine was administered in conjunction with the cue (Caggiula *et al.*, 2001). In fact, a nicotine-associated cue alone supported responding at equivalent levels to nicotine itself (Palmatier *et al.*, 2006). Furthermore, combining contingent cues with contingent nicotine had a synergistic effect on response rates, such that nicotine and the contingent cue together sustained levels of responding greater than their additive effects. In addition, in a two-lever procedure, where one lever was reinforced with nicotine while the other was reinforced with a visual stimulus, responding for the visual stimulus lever was significantly higher than responding for the nicotine, and was equal to responding in a single-lever procedure for nicotine together with the visual cue (Palmatier *et al.*, 2006). Altogether, this research demonstrates that animals respond preferentially for drug combined with a cue compared with drug alone. It should be noted, however, that animals, especially mice, will respond for visual stimuli in the absence of drug reinforcement; this is typically most robust when randomly varied light responses are used to maintain novelty in sensation-seeking paradigms (Olsen and Winder, 2009). This would suggest that the act of lever pressing can be reinforcing in and of itself. Importantly, however, under these contingencies mice typically take longer to acquire good discrimination between active and inactive levers compared with drug self-administration.

The reason for enhanced drug intake when in combination with a cue relates to the cue itself becoming a conditioned reinforcer (e.g. Zimmerman, 1957; Kelleher, 1966 – see Figure 1A). In this situation, the cue acquires innate reinforcing properties because of its association with the primary drug reinforcer. It is known that reward-associated stimuli acquire rewarding properties independent of the primary reinforcer, as rats trained to respond for sucrose paired with a cue will subsequently work to obtain cue presentations even when the number of associated sucrose deliveries declines to very low levels (Di Ciano and Everitt, 2004). In the case of drug self-administration, conditioned reinforcement from the cue acts together with primary reinforcement from the drug to enhance drug-seeking behaviour (Caggiula *et al.*, 2009). Critically, this effect is observed across a range of drug classes. For example, the presence of a cue enhanced acquisition of a lever press response for either cocaine or heroin (Di Ciano and Everitt, 2004). Furthermore, extinction of cocaine seeking in the presence of these response-contingent CSs was delayed compared with in its absence (Arroyo *et al.*, 1998), indicating that cues acting as conditioned reinforcers can cause a persistence in drug-seeking behaviour even in the absence of the primary reinforcer. This dissociation between primary and conditioned reinforcement in drug seeking has also been demonstrated pharmacologically. Administration of 2-methyl-6-(phenylethynyl)pyridine (MPEP), an mGlu5 negative allosteric modulator (NAM), decreased responding on the nicotine lever in a two-lever procedure, but had no effect on responding for the visual cue (Palmatier *et al.*, 2008). This suggests that mGlu5 are important for the primary reinforcing effects, but not the conditioned reinforcement of CSs. Conversely, the opioid receptor antagonist naltrexone had no effect on self-administration of nicotine alone, but decreased responding for the visual stimulus when nicotine was replaced with saline (Liu *et al.*, 2009). Evidently, the neurobiology underpinning the primary and secondary reinforcement of drug-seeking behaviour involves at least some separate mechanisms, and this should be taken into consideration when designing treatments for drug addiction.

In addition to acting as conditioned reinforcers, drug-paired CSs can also enhance drug intake when functioning as discriminative stimuli (Estes, 1948). For instance, rats that

Table 4

Opiate-seeking behaviour: effect of pharmacological agents on cue-, stress- and drug-primed reinstatement

System	Reference	Cue	Stress	Prime
Adenosine receptors				
A_{2A} receptor antagonist				
DMPX	Yao *et al.*, 2006			Decreased
Adrenoceptors				
α_2 adrenoceptor agonist				
Clonidine	Shaham *et al.*, 2000		Decreased	
Corticosterone synthesis inhibitor				
Metyrapone	Shaham *et al.*, 1997		No effect	No effect
Cannabinoid receptors				
CB_1 receptor antagonist				
SR 141716A (Rimonabant)	Fattore *et al.*, 2005			Decreased
	De Vries *et al.*, 2003	Decreased		Decreased
	Fattore *et al.*, 2003			Decreased
Dopamine				
D_1 receptor antagonist				
SCH-23390	Shaham and Stewart, 1996		No effect	Decreased
	Tobin *et al.*, 2008		Decreased	
D_2 receptor antagonist				
Raclopride	Shaham and Stewart, 1996		No effect	Decreased
	Tobin *et al.*, 2008		No effect	
D_3 receptor antagonist				
NGB 2904	Tobin *et al.*, 2008		No effect	
Mixed dopamine antagonist				
Flupenthixol decanoate	Shaham and Stewart, 1996		Decreased	Decreased
Levo-tetrahydropalmatine (l-THP)	Yue *et al.*, 2012			Decreased
GABA				
$GABA_B$ receptor agonist				
Baclofen	Spano *et al.*, 2007			Decreased
Neuropeptides				
Corticotropin-releasing factor (CRF)				
CRF antagonist				
α-Helical CRF	Shaham *et al.*, 1997		Decreased	Decreased
	Shalev *et al.*, 2006		Decreased	
CP-154,526	Shaham *et al.*, 1998		Decreased	
Ghrelin				
Ghrelin receptor antagonist				
[D-Lys-3]-GHRP-6	Maric *et al.*, 2011b		No effect	
Neuropeptide Y (NPY)				
NPY Y_5 receptor antagonist				
Lu AA33810	Maric *et al.*, 2011a		Decreased	
NPY Y_1 receptor antagonist				
BIBO 3304	Maric *et al.*, 2011a		No effect	
Opioids				
Antagonist				
Naltrexone	Shaham and Stewart, 1996		No effect	Decreased
	Fattore *et al.*, 2005			Decreased
Orexin				
OX_1 receptor antagonist				
SB-334867	Smith and Aston-Jones, 2012	Decreased		No effect
Vasopressin				
Vasopressin V_{1b} receptor antagonist				
SSRI49415	Zhou *et al.*, 2007		Decreased	Decreased
Other manipulations (mixed actions)				
Acamprosate	Spanagel *et al.*, 1998		No effect	No effect

Table 5

Cannabinoid-seeking behaviour: effect of pharmacological agents on cue-, stress- and drug-primed reinstatement

System	Reference	Cue	Stress	Prime
Adenosine receptors				
A_{2A} receptor antagonist				
MSX-3	Justinova *et al.*, 2010			No effect
Cannabinoid receptors				
Cannabinoid receptor antagonist				
SR141716A (Rimonabant)	Justinova *et al.*, 2008	Decreased		Decreased
	Spano *et al.*, 2004			Decreased
Opioid receptors				
Opioid receptor antagonist				
Naloxone	Spano *et al.*, 2004			Decreased
Other manipulations (mixed actions)				
Ro 61-8048	Justinova *et al.*, 2013	Decreased		Decreased

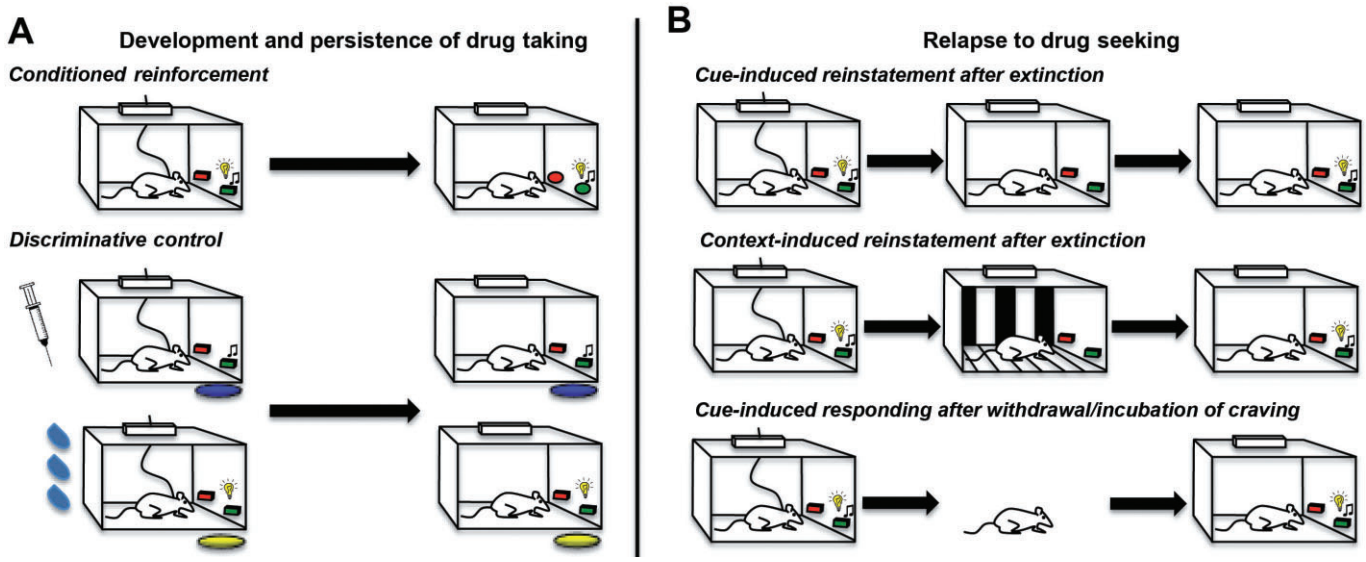

Figure 1

Animal models for cue-induced drug taking and drug seeking. Panel A shows preparation used to study drug taking. These are variations of the self-administration model, designed specifically to examine the effect of cue on drug taking. In conditioned reinforcement, a response-contingent cue comes to possess reinforcing effects, and is able to enhance drug taking and support acquisition of a new response. In discriminative control, a cue that signals availability of drug promotes responding (in the presence or absence of further drug reinforcement), while a cue that signals availability of saline or water inhibits responding. Panel B shows preparations used to study relapse to drug seeking. In cue-induced reinstatement, the response is extinguished in the absence of the cue, and then recovered by re-pairing the cue with the drug-seeking instrumental response. In context-induced reinstatement, the response is extinguished in a distinctively different context from that used for self-administration, and recovered by re-exposure to that original drug-taking context. In incubation of craving, rats are subjected to a period of enforced abstinence, but with no further behavioural training. Cues are subsequently able to support responding even in the absence of further drug reinforcement. Typically, there is an increase in cue-induced drug seeking after a period of abstinence. It should be noted that both conditioned reinforcers and discriminative cues (Panel A) are able to produce drug seeking after extinction or withdrawal (Panel B).

were initially presented with a tone followed by food, and then trained to lever press for food, subsequently responded at higher levels when the cue was present than when it was absent (Estes, 1948). Since this initial finding, similar results have been produced for drugs of abuse. For example, rats trained to lever press for alcohol or cocaine in the presence of S+, and water or saline in the presence of S–, subsequently showed higher responding in the presence of the S+ (Katner *et al.*, 1999; Weiss *et al.*, 2000; Suto *et al.*, 2013). Moreover, the presence of the discriminative cue increased responding

under maintenance conditions where the drug was available, or under extinction conditions where it was not (Panlilio *et al.*, 1996; 2000a,b). This effect is closely linked with the release of glutamate in the nucleus accumbens (NAc). Specifically, microdialysis has revealed that glutamate levels in the NAc core and shell regions were elevated during the presence of an olfactory stimulus that signalled cocaine availability (Hotsenpiller *et al.*, 2001; Suto *et al.*, 2013), and depressed during the presence of an alternate odour that signalled cocaine omission (Suto *et al.*, 2013). Furthermore, antagonism of ionotropic (NMDA/AMPA) glutamate receptors by kynurenate microinjections in the NAc core, but not shell, decreased responding in the presence of the S+ (Suto *et al.*, 2013).

A caveat to the discriminative cue paradigm is that it confounds the influence of a discriminative stimulus (the S+) with the effect of a response-contingent CS+. Nevertheless, a discriminative stimulus alone appears sufficient to guide and energize drug intake and this should be taken into consideration in the clinical setting. It is important to note that discriminative cues signal not only the availability, but also the non-availability of drug (Suto *et al.*, 2013). This reflects reports that heroin users and smokers experience reduced craving for drugs in particular circumstances in which they know that the drug is not available (Robins *et al.*, 1974; Dar *et al.*, 2010). This is an important therapeutic consideration, as stimuli present during detoxification may come to specifically signal non-availability of the drug. Hence, although craving may be reduced in the presence of these stimuli, it may return in their absence.

Cue itself becomes consumed. Cues that have become conditioned reinforcers not only enhance drug intake when presented in combination with the primary reinforcer, but also acquire intrinsic rewarding effects such that they themselves will be consumed. For example, rats were trained to lever press for cocaine delivered in conjunction with a visual CS before a second-order schedule of reinforcement was introduced and infusions of cocaine were gradually decreased to the point where rats were responding almost exclusively for the CS alone (Bäckström and Hyytiä, 2006; 2007; Di Ciano, 2008a). In fact, rats will respond under these schedules for 10 days or more (Arroyo *et al.*, 1998; Bäckström and Hyytiä, 2006). Conditioned reinforcement can also be demonstrated via the ability of a drug-paired cue to support acquisition of a novel response (Figure 1A). For example, rats were trained to nose poke for i.v. cocaine or heroin delivery paired with a light CS. Following this, the rats were trained to lever press for the light CS, in the absence of any further cocaine delivery. Rats preferentially pressed a lever that resulted in light delivery compared with a lever that had no consequences (Di Ciano and Everitt, 2004). These findings indicate that drugs of abuse can impart reinforcing properties on discrete cues.

In fact, drugs of abuse not only confer, but also enhance conditioned reinforcement properties (Caggiula *et al.*, 2001; Olausson *et al.*, 2004a,b; Palmatier *et al.*, 2006). For example, when a CS has been shaped using food pellets as a reinforcer, rats will subsequently respond more to obtain presentations of these cues while under the influence of continuous nicotine infusion, compared with infusion of saline (Weaver *et al.*, 2012). In effect, this is complementary to the situation where conditioned CSs act to enhance drug intake. Here, the drug is not contingent on lever press, but is rather acting to enhance intake of the cue. Importantly, this effect is neither dependent on the CS presentation being contingent with drug infusion, nor on drug delivery being contingent on lever press, but only on the CS presentation being contingent on the response (Donny *et al.*, 2003; Weaver *et al.*, 2012). The ability of nicotine to enhance the strength of the reinforcer is dependent on the pre-existing strength of the conditioned reinforcer itself (Caggiula *et al.*, 2009). For instance, a cue that has been previously paired with sucrose is more sensitive to the enhancing properties of nicotine than an unpaired cue (Chaudhri *et al.*, 2006), while a cue that possesses more innate reinforcing effects is more sensitive than a cue that is less innately reinforcing (Palmatier *et al.*, 2007). Therefore, responding is higher not because of a contiguous relationship between CS presentation and drug delivery, but rather due to the fact that the CS is rendered more reinforcing by the presence of the drug, and hence, is able to support higher levels of responding.

Nicotine is not the only drug of abuse that possesses this cue reinforcement-enhancing property. Cocaine sensitization can also increase the reinforcing value of a drug-associated CS. Rats trained to nose poke for cocaine paired with a light CS were subsequently able to acquire a lever press response that was reinforced with the conditioned CS. This effect was facilitated if the rats were given five daily injections with cocaine between the initial and the second-order training, compared with non-sensitized rats (Di Ciano, 2008b). Similarly, amphetamine sensitization between first-order and second-order conditioning for food pellets results in facilitated acquisition of the novel response (Wyvell and Berridge, 2001). Cues are more rewarding in the presence of amphetamine; so non-contingent amphetamine increased responding for visual cues possessing innate reinforcing value (Glow and Russell, 1973). Micro-injection of amphetamine into the NAc shell immediately prior to test likewise facilitated the acquisition of second-order conditioning for food pellets (Wyvell and Berridge, 2000). Therefore, drugs of abuse are able to enhance the reinforcing effects of cues, most likely via their influence on dopaminergic pathways (Berridge and Robinson, 1998).

Together, this research indicates that by virtue of their association with drugs of abuse, environmental stimuli acquire reinforcing effects, and animals will work to obtain and consume them. Furthermore, drugs of abuse actually potentiate these reinforcing effects in a way that is not observed with naturally occurring reinforcers. This phenomenon is observed not only in animal models, but also in the human scenario. Human smokers receiving i.v. nicotine alone report dissatisfaction and ongoing craving for cigarettes compared with smokers that received i.v. nicotine in combination with de-nicotinized cigarettes. Thus, craving is experienced for the cues associated with smoking as much as for the nicotine itself (Rose *et al.*, 2000). These observations go some way to explaining why drug seeking, even for drugs such as nicotine that possess only weak reinforcing effects, can be so persistent. Moreover, drug-paired stimuli such as the smell of smoke or the packaging of a cigarette box, by definition, tend to occur in combination with drug delivery. If individuals will work to obtain these cues, then intake of

the drug itself is likely to occur as a matter of course. Hence, there is further reinforcement of the drug seeking, and the patterns of behaviour become more firmly entrenched.

Role of cues in relapse-like behaviour following extinction

Discrete cues. As well as enhancing and maintaining drug intake, discrete cues associated with drug use will reliably recover responding following extinction training, even in the absence of any further primary reinforcement (Davis and Smith, 1974 – see Figure 1B). Frequently, the CS is only presented after the subject has emitted a drug-seeking response; hence, the first presentation is dependent on the animal performing an initial response. In this situation, the cue is a conditioned reinforcer, as described previously. Discrete cue-induced reinstatement is a robust effect that has been observed across many drug classes, including psychostimulants (See *et al*., 1999; See, 2005), alcohol (Lawrence *et al*., 2006) and nicotine (Liu *et al*., 2009).

Discriminative cues. Discriminative cues will also reinstate extinguished drug-seeking behaviour. Rats trained to self-administer drug under S+/CS+ conditions or water under S–/CS– conditions, and then extinguished with no cues present, will show an increase in responding when tested under S+/CS+ conditions in the absence of any further drug (Liu and Weiss, 2002; Williams and Schimmel, 2008; Liu *et al*., 2009). In the S–/CS– condition, responding remains low. Here again, responding is being reinstated at least in part owing to the conditioned reinforcement provided by the cue.

However, it is important to note that in the discriminative paradigm, the S+/S– is present upon initiation of session, so it may be that the discriminative conditions are acting not only to provide ongoing conditioned reinforcers, but also as contextual cues to precipitate responding (Ciccocioppo *et al*., 2002; 2003; Burattini *et al*., 2008). In line with this, the S+ can be sufficient to reinstate drug-seeking behaviour (Katner *et al*., 1999). Furthermore, in some experimental procedures, subjects are given a non-contingent presentation of the CS+/CS– upon initiation of the reinstatement session. For example, rats trained to lever press for an ethanol solution in the presence of a light/clicker CS complex were then extinguished in the absence of this cue. They were then tested in a within-session design, where they responded first under extinction conditions and were then given repeated, non-contingent presentation of the alcohol-paired CS. The number of alcohol-seeking responses emitted after presentations of the cue complex was higher than in the period before the cue (Bienkowski *et al*., 1999). Here, subjects are not consuming the cue itself, as in conditioned reinforcement, but rather the presentation of the cue initiates drug seeking despite extinction and continuing non-reinforcement. Therefore, the cues possess properties of incentive motivation that are able to attract the animal to perform the drug-seeking response. In this way, like contextual cues, the CS+ serves as a background to guide behavioural output.

Contextual cues. Contextual cues are also known to precipitate relapse-like behaviour. These stimuli generally differ from discrete and discriminative cues in that they are complex configurations of environmental stimuli that have no direct contingency with behaviour, but rather serve as a backdrop to drug-taking activities. Nevertheless, contextual cues serve as important mediators of drug-seeking behaviour. As the drug user learns that certain environments are associated with drug availability, these contexts can then function to modulate drug-taking actions (Bouton, 2002). The effect of contextual cues on reinstatement can be modelled using a behavioural paradigm known as 'renewal', where a learned association that has been extinguished in an alternate context is recovered following return to the original context (Welker and McAuley, 1978; Bouton and Bolles, 1979). Renewal, or context-induced reinstatement has been reliably extended to the case of instrumental responding for a drug reinforcer across a range of drug classes (e.g. Crombag and Shaham, 2002; Zironi *et al*., 2006; Bossert *et al*., 2007; Hamlin *et al*., 2007; for reviews, please refer to Crombag *et al*., 2008a,b; Janak and Chaudhri, 2010).

Contextual control (both internal and external) of instrumental extinction has in fact been extensively studied in the past decade, and the results have been reviewed comprehensively elsewhere (Pinel and Treit, 1978; Pellow *et al*., 1985; Powell *et al*., 1993a,b; Crombag *et al*., 2008a,b; Janak and Chaudhri, 2010; Luo *et al*., 2011; Millan *et al*., 2011; Mihindou *et al*., 2012; Myers and Carlezon, 2012; Price *et al*., 2012). However, it is worth highlighting that context-induced reinstatement clearly illustrates that extinction training does not erase the original learning, but rather results in a new inhibitory learning, that creates a context-dependent 'mask' over the original learned behaviour (Bouton and Swartzentruber, 1991; Bouton, 2002). In effect, as a result of extinction training, the meaning of the response or the stimulus becomes ambiguous. The context serves to resolve this ambiguity in order to express the appropriate behaviour (Bouton, 2002). The outcome of this is that extinction training is highly context specific. Mere removal from the extinction context can lead to a return of the original behaviour, even where that context has never previously been paired with the reinforcer (Bouton *et al*., 2011), although it should be noted that this effect is much weaker and less robust than the reinstatement that occurs when the animal is returned to the original context after extinction in a different context (e.g. Nakajima *et al*., 2000). Nevertheless the role of context in expression of extinguished behaviour has important therapeutic implications (Tiffany and Conklin, 2002), which will be discussed in more depth in section entitled *Cue extinction is context specific*. Furthermore, via the context-induced reinstatement model, it has also been established that relapse to drug seeking produced in response to discrete cues versus contextual cues operates via a separate, although overlapping circuitry (Fuchs *et al*., 2004; Bossert *et al*., 2007; Chaudhri *et al*., 2010). This is an important observation because it implies that contextual cues and discrete cues mediate drug seeking via distinct mechanisms (Zhou *et al*., 2005), which should be considered when developing therapeutic strategies for overcoming substance-abuse disorders.

Role of cues in relapse-like behaviour following abstinence

While the extinction-reinstatement procedure is widely utilized in addiction research, it is important to note that a

relatively small proportion of human addicts actually undergo rehabilitation as modelled by instrumental extinction (Shaham *et al.*, 2003). While the neural circuitry that stimulates the desire to cease drug taking in humans may share circuits involved in the expression of extinction in rodents, this may not be the most ethologically valid analogue of the human scenario (Peters *et al.*, 2008). Indeed, although instrumental extinction is certainly more effective in reducing responding than withdrawal (e.g. Myers and Carlezon, 2010), detoxification in the human population more commonly involves a period of enforced or voluntary abstinence. Therefore it is important to consider animal models of withdrawal when investigating the influence of cues on drug-seeking behaviour.

In fact, the ability of a cue to reinstate extinguished responding will survive a long period of abstinence, even if extinction training was conducted prior to withdrawal. For example, in a study by Jupp *et al.* (2011), inbred alcohol-preferring rats were trained to lever press for alcohol under S+/CS+ conditions, and then extinguished in the absence of any cues. Following this, one group of animals was subjected to cue-induced reinstatement on the day immediately following the last day of extinction, while the second group was housed without any further exposure to alcohol or alcohol-associated cues for a period of 5 months before undergoing the same reinstatement test. Both the extinction only and the extinction plus abstinence group showed equivalent reinstatement, despite the lengthy delay for the second group, such that on a behavioural level there was no difference in the ability of the cue to reinstate responding (Jupp *et al.*, 2011). Pharmacological analyses indicated that there were also similarities in the neural substrates for cue-induced responding before and after a period of abstinence. Specifically, as with cue-induced reinstatement immediately after extinction (Lawrence *et al.*, 2006; Jupp *et al.*, 2011), reinstatement following extinction and abstinence appeared to be orexin-dependent. However, quantification of the neural correlates of this effect revealed increased activity in the infralimbic, prelimbic, orbitofrontal and piriform cortices after protracted abstinence over and above levels seen after immediate reinstatement. Furthermore, administration of an orexin OX_1 receptor antagonist resulted in a decrease in activation of the NAc core in the immediate reinstatement group, but not the delayed group. These effects were presumably due to differential processing of the cues as a result of the abstinence period, given that responding levels were equivalent between the two groups (Jupp *et al.*, 2011). Therefore, changes to the underlying processing of drug-associated cues seemingly occurred as a result of the abstinence period.

In addition to reinstatement of drug seeking following both extinction and abstinence, laboratory animals will likewise show robust responding for drug-associated cues after extended periods of withdrawal without any extinction training (Brown *et al.*, 2009; 2012; Adams *et al.*, 2010; Cahir *et al.*, 2011; Fischer *et al.*, 2013 – see Figure 1B). Moreover, periods of withdrawal have actually been associated with subsequent increases in cue-induced drug seeking. This effect is known as incubation of craving (Grimm *et al.*, 2001; Pickens *et al.*, 2011; Dikshtein *et al.*, 2013), because cue-induced reward seeking is seen as an operational measure of craving (Markou *et al.*, 1993). Incubation of craving is observed across a range of behavioural reinforcers, including natural rewards as well as drugs of abuse. For instance, rats trained to respond for sucrose (Grimm *et al.*, 2005; 2012) or saccharin (Aoyama *et al.*, 2014) paired with a light-tone CS showed greater cue-induced reward seeking after 30 days compared with 1 day of enforced abstinence from the sweetener. Similarly, increases in drug seeking after periods of abstinence have been repeatedly demonstrated (reviewed in Lu *et al.*, 2004), and are also robust across different drugs of abuse, including alcohol, nicotine, heroin, methamphetamine and cocaine (e.g. Li *et al.*, 2008; Pickens *et al.*, 2011; Theberge *et al.*, 2013). Critically, incubation of craving, also referred to as delayed onset craving, is also observed in human drug users (Gawin and Kleber, 1986; Bedi *et al.*, 2011; Wang *et al.*, 2013). Although in both preclinical and clinical models this effect decreases after more extended periods of abstinence, human drug users have been shown to exhibit increases in cue-related cravings during the first few months of withdrawal (Lu *et al.*, 2004; Wang *et al.*, 2013). Therefore, animal models that examine the effect of a period of abstinence on cue-induced drug seeking possess implicit translational value.

Role of the mGlu5 receptor in acquisition, extinction and reinstatement of cue-mediated drug seeking

Glutamatergic transmission has a clear role in cue-mediated expression of drug-taking and -seeking behaviours, as demonstrated by both animal models and human experiments. For example, injections of the mGlu5 NAM 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine (MTEP) impaired the ability of a cue to acquire conditioned reinforcing effects in mice, but had no effect on the expression of these properties, and did not impair either the acquisition or the expression of discriminative control over reward seeking (O'Connor *et al.*, 2010a). The NMDA partial agonist D-cycloserine has shown great promise as an adjunct to therapy targeted at drug-associated cues in human clinical trials (Tomek *et al.*, 2013). Conversely, ionotropic glutamate receptor antagonists can decrease reinstatement produced by both discriminative (Bäckström and Hyytiä, 2004) and discrete cues (Di Ciano and Everitt, 2001; Bäckström and Hyytiä, 2006; Mahler *et al.*, 2013).

In particular, the mGlu5 receptor appears to play an important role in mediating the maintenance and the reinstatement of drug seeking guided by drug-associated stimuli, although studies examining pharmacological manipulation of mGlu5 activity have produced mixed findings. For instance, a number of groups have investigated the effect of inhibiting mGlu5 receptor activity on contextual cue-modulated drug-seeking behaviour, using a conditioned place preference (CPP) model. In this procedure, administration of the drug of abuse is paired with distinct contextual cues in one chamber, while saline is paired with distinct contextual cues in another chamber, on separate trials. On test day, animals are allowed unrestricted access to both chambers in the absence of primary reinforcement. More time spent on the side previously paired with drug administration is considered a measure of craving associated with the rewarding properties of the drug and drug-associated contextual cues. Some studies report that the mGlu5 receptor NAM MPEP attenuated the acquisition of CPP using morphine (Popik and

Wrobel, 2002; Aoki *et al.*, 2004) and cocaine (Chiamulera *et al.*, 2001; McGeehan and Olive, 2003), and reduced the expression of CPP for morphine (Popik and Wrobel, 2002; Herzig and Schmidt, 2004; Veeneman *et al.*, 2011), amphetamine (Herzig *et al.*, 2005), methamphetamine (Herrold *et al.*, 2013), nicotine (Yararbas *et al.*, 2010) and alcohol (Lominac *et al.*, 2006). This work suggests that MPEP attenuates the rewarding effects of drugs of abuse, or the contextual cues associated with them.

However, it has also been shown that inhibiting the activity of mGlu5 receptors can potentiate rather than attenuate cue-mediated drug-seeking behaviour. For example, administration of MPEP during acquisition resulted in a leftward shift in the dose required to induce CPP for heroin (van der Kam *et al.*, 2009), nicotine (Rutten *et al.*, 2011) and cocaine (Rutten *et al.*, 2011). In line with this, Bird and colleagues (2014) recently showed that despite showing similar self-administration of cocaine on a FR compared with wild-type (WT) controls, mice lacking the mGlu5 receptor displayed enhanced responding on a progressive ratio schedule supported by a discrete cue. It may be the case that rather than attenuating the rewarding or reinforcing properties of drugs of abuse or the cues that become associated with them, inhibiting the activity of mGlu5 receptors may be potentiating these effects. However, yet others have reported no effect of MPEP on cocaine CPP expression (Herzig and Schmidt, 2004), and similarly, no differences in CPP between genetically modified mGlu5 receptor-deficient mice and WT controls (Chesworth *et al.*, 2013; Bird *et al.*, 2014). Evidently, the role of mGlu5 receptors in the acquisition and maintenance of cue-mediated drug-seeking behaviour is not clear-cut.

There is also evidence for the role of mGlu5 receptors in extinction of cue-mediated drug-seeking behaviour, although overall findings are again conflicting. Using a CPP model, a number of studies report that positive allosteric modulation of mGlu5 receptors enhanced contextual cue extinction (Dhami and Ferguson, 2006; Gass and Olive, 2009; Ribeiro *et al.*, 2009; Cleva *et al.*, 2011). In line with this, genetically modified mGlu5-deficient mice showed a marked deficit in the extinction of a cocaine-conditioned contextual cues (Bird *et al.*, 2014). Similarly, in a cocaine self-administration model, systemic injections of MTEP following context only extinction sessions reduced the effectiveness of this treatment to attenuate cocaine-primed reinstatement (Kim *et al.*, 2014). However, in another study examining extinction of cocaine self-administration contextual cues, rats that received discrete cue extinction showed no difference in tissue and synaptosomal mGlu5 and Homer 1b/c receptor levels compared with a saline self-administration group (Ghasemzadeh *et al.*, 2009b). Yet again, a later study found a decrease in postsynaptic density levels of mGlu5 in the dorsomedial prefrontal cortex of animals in the contextual cue and lever extinction group but not the home cage group, when compared with the saline self-administration animals (Ghasemzadeh *et al.*, 2011). It may be the case mGlu5 receptor signalling is required for extinction learning; however, plasticity associated with this conditioning ultimately results in an overall decrease in mGlu5 receptor function. This means that positive modulation of mGlu5 receptors during conditioning might facilitate extinction because of receptor desensitization. Alternatively, mGlu5 receptors may play a different role depending on what drug-associated environmental stimuli are being extinguished, that is, discrete versus contextual cues. Evidently further research is required to more fully elucidate the role of mGlu5 receptor in extinction learning.

Importantly, mGlu5 receptors are also involved in cue-mediated reinstatement of drug seeking. For example, specific mGlu5 knockdown on striatal D1-expressing neurons of mice lead to attenuated cue-induced reinstatement of cocaine seeking after extinction, despite animals showing intact capacity to learn a Pavlovian association between the CS and food delivery (Novak *et al.*, 2010). Thus, mGlu5 receptor knockdown seemed to specifically impair the ability of the drug-associated cue to act as a conditioned reinforcer after extinction. Administration of mGlu5 NAMs also decreased cue-induced reinstatement for alcohol seeking (Bäckström and Hyytiä, 2004; Schroeder *et al.*, 2008) and cocaine seeking (Bäckström and Hyytiä, 2006; 2007; Martin-Fardon *et al.*, 2009). Glutamate transmission at mGlu5 and AMPA receptors within striatal neurons appears to be particularly important for cue-mediated responding after extinction (Bäckström and Hyytiä, 2007). Interestingly, mGlu5 receptors interact with adenosine 2_A ($A2_A$) receptors in mediating cue-induced drug seeking, as a combination of sub-threshold doses of antagonists to these receptors prevented alcohol seeking under S+/CS+ conditions (Adams *et al.*, 2008).

As with cue-induced reinstatement after extinction (Bäckström and Hyytiä, 2006; 2007) systemic application of MTEP reduces morphine-seeking under S+/CS+ conditions after a 3 week period of abstinence in mice (Brown *et al.*, 2012). MTEP and a cannabinoid CB_1 receptor antagonist also showed additive effects indicating that although both mGlu5 and CB_1 receptors are important, they mediate their influence on cue-induced alcohol seeking via separate mechanisms (Adams *et al.*, 2010), in contrast to the synergy observed between mGlu5 and A2A receptors (Adams *et al.*, 2008).

Based on these findings, mGlu5 receptor ligands may provide important adjuncts to behavioural addiction treatment. Such drugs are already in clinical trial for other disorders, including schizophrenia (Lindsley and Stauffer, 2013) and Parkinson's disease (Duty, 2012; Vallano *et al.*, 2013). They are now being considered as potential treatments for addiction, although the cognitive effects of mGlu5 are complex, especially as they are also important for extinction (Cleva *et al.*, 2011). Thus, care needs to be taken that a drug that may reduce drug seeking acutely does not also interfere with behavioural treatments involving extinction. Nevertheless, mGlu5 receptor ligands remain a promising candidate for clinical trials (Olive, 2010).

What does the cue actually represent? Conditioned reinforcement versus incentive motivation

Despite the many advantages of using a self-administration reinstatement model of cue-mediated drug-seeking behaviour, many of the procedures described earlier confound Pavlovian and instrumental contingencies, as the CS is paired with drug delivery in a response-contingent manner (LeBlanc

et al., 2012). Thus, it is not clear whether cue-induced reinstatement necessarily occurs because the drug-associated CS is acting as a conditioned reinforcer, or whether it is invigorating instrumental drug seeking via incentive motivational properties acquired as a result of associations with the drug. In many designs, both a discriminative cue and a response-contingent CS+ is present, and so drug seeking may be elicited via incentive motivational properties of the S+, or alternatively animals may be responding for cue, acting as a CS (Caggiula *et al.*, 2009).

A likely scenario is that drug-associated CSs elicit responding both via incentive motivational properties and by way of acting as conditioned reinforcers. Earlier we described how a drug-paired cue acquires conditioned reinforcement properties that allow it to maintain responding in the absence of further primary reinforcement (Di Ciano, 2008a), as well as support acquisition of new responses (Di Ciano and Everitt, 2004; Di Ciano, 2008b). LeBlanc *et al*. (2012) provided evidence for the former when they demonstrated Pavlovian-to-instrumental transfer (PIT) using cocaine as a reinforcer. In PIT, a cue that has been previously paired with a particular outcome is able to facilitate or 'energize' operant responding that has been trained to the same outcome (Zanich and Fowler, 1978; Rescorla, 1994; Dickinson *et al.*, 2000; Crombag *et al.*, 2008a,b). In the study by LeBlanc *et al*. (2012), this was achieved using a drug of abuse as the reinforcer. Rats were first given repeated pairings of an auditory CS (the CS+) with a delivery of cocaine. A second cue (the CS–) was presented in a non-reinforced manner. Rats were then trained to self-administer cocaine using a seeking-taking chain (Olmstead *et al.*, 2000), in the absence of any discrete cues. Subsequent responding was greater in the presence of the CS+ than the CS–. That is, PIT had occurred, because the previously cocaine-paired cue was able to facilitate responding for cocaine. This finding illustrates that the drug-paired cues facilitate drug-taking behaviour by inducing a state of incentive motivation (LeBlanc *et al.*, 2012).

In support of this observation, it has also been shown that CSs are able to acquire motivational properties when trained separately to the operant response. For example, when rats were initially conditioned to lever press for morphine in the absence of a cue, then received passive presentations of the cue paired with morphine infusion, that cue was subsequently able to reinstate the extinguished operant response in the absence of further drug reinforcement (Davis and Smith, 1974; Kruzich *et al.*, 2001). These drug-paired cues reinstated responding to a greater extent than a novel cue or an unpaired cue, demonstrating that the effect does not arise solely because of inherent motivational properties of the cue (Kruzich *et al.*, 2001; Yager and Robinson, 2013). However, this protocol reveals critical individual differences, in that only 'sign trackers' (rats that preferentially approached a food-associated cue rather than the food cup into which the reinforcer was delivered) showed this pattern of response. On the other hand, 'goal trackers' (rats that showed the opposite behavioural pattern) tended to show equal reinstatement to the unpaired and paired cues (Yager and Robinson, 2013). Taken together, these findings suggest that individual differences can play an important role in the way drug-associated or novel cues are processed in the context of drug seeking, but regardless, these cues are powerful mediators of behaviour.

We have described how animal models have been used to elucidate the role of environmental stimuli in developing and maintaining drug use, and in precipitating a return to drug seeking following a drug-free period. Three main models were discussed: drug self-administration, reinstatement of drug seeking, and incubation of craving, or cue-induced responding after a period of withdrawal. The first of these provides a model for the acquisition and maintenance of drug-seeking behaviour. The second two provide models for relapse-like behaviour, although it should be noted that distinct from the human relapse scenario, reinstatement in an animal model does not involve actual drug intake, but provides purely a measure of drug seeking. A summary of the different models, and the role of the cue within them, is illustrated in Figure 1. In all cases, the drug seeking involves an instrumental relationship between a particular response and drug delivery. However, in all cases, the presence of a cue is pivotal for facilitating or precipitating responding. Within each of these models, a cue may acquire conditioned reinforcing effects, and hence be consumed itself, it can promote (or inhibit) drug seeking by acquiring discriminative control over the response. Finally, it can acquire incentive motivational properties that promote approach and energize drug seeking. Common to these psychological mechanisms is that cues associated with drugs of addiction are able to motivate and facilitate instrumental drug seeking and intake. It is these properties that allow drug-associated cues to support drug seeking after periods of inhibitory extinction training, or abstinence.

Drug-associated cues as therapeutic targets

Extinction of cues associated with drugs

Historically, much research concerned with reducing drug-seeking behaviours has focussed on delineating the neural circuitry underlying instrumental extinction (see Millan *et al.*, 2011; Bossert *et al.*, 2013). Although this work has broadened our understanding of the mechanisms underlying drug-seeking behaviour, it may have only limited translational applicability, as instrumental extinction would be difficult to apply in the human situation. (Mihindou *et al.*, 2012; Buffalari *et al.*, 2013).

In fact, behavioural treatment for substance-abuse disorders in the clinic mostly involves cue exposure therapy (CET) (Rohsenow *et al.*, 2001; Loeber *et al.*, 2006). CET comprises of repeated exposure to cues associated with the drug experience, without any drug availability. The desired outcome of CET is reduction in cue reactivity, craving, anxiety and ultimately relapse triggered by the drug-related cue (Hodgson and Rankin, 1976). When CET was first trialled on alcoholics, it was found that exposure to both imagined and real alcohol-associated cues could delay desire for and the drinking of an alcoholic beverage (Rankin *et al.*, 1983). Since CET has been adapted and trialled against many different drugs of abuse, including nicotine, opiates and psychostimulants (Prisciandaro *et al.*, 2013; Unrod *et al.*, 2013). Additionally, new techniques including virtual reality and online capacity are being used to increase the complexity of the cue

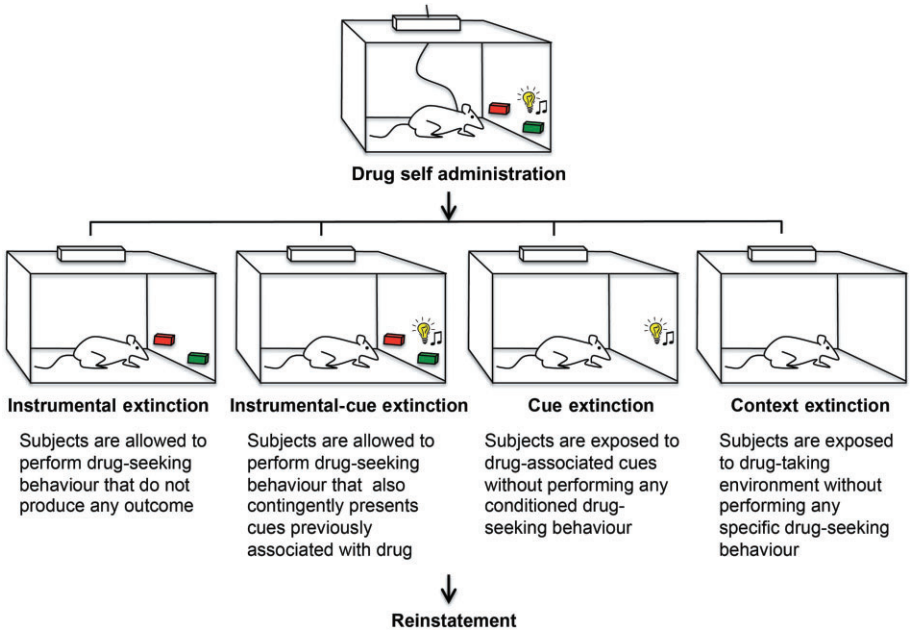

Figure 2

Different extinction protocols leading to a change in drug seeking. All of these represent variants of the extinction-reinstatement model (Figure 1B), which allow researchers to examine the effect of extinguishing drug-associated environmental stimuli on subsequent drug-seeking behaviour.

presentations and therapy accessibility (Culbertson *et al.*, 2010; Choi *et al.*, 2011; Ferrer-García *et al.*, 2013).

CET essentially relies on the concept of 'cue extinction', that is, the reduction of conditioned drug-seeking behaviours because of non-reinforced presentations of the drug-associated cue. For the purpose of this review, we are limiting the definition of cue extinction as repeated presentations of the cue that is not contingent to drug-seeking responses (Figure 2), to avoid confounding effects of instrumental extinction that occurs with response-contingent cue exposure. Surprisingly, there have been few attempts at studying cue extinction separately from instrumental extinction in the laboratory. Buffalari *et al.* (2013) explicitly compared the effectiveness of instrumental extinction, instrumental-cue extinction, cue extinction, and context extinction in reducing cue-induced reinstatement of cocaine seeking (see Figure 2). In that study, the instrumental-cue extinction group displayed the least reinstatement, followed by the instrumental extinction group. The cue extinction and context extinction reinstated to the greatest extent. This suggests that without instrumental extinction, cue extinction is not as effective in reducing relapse-like behaviour. However, it should be noted that cue extinction involved 23 presentations of the cocaine-associated CS, whereas the instrumental-cue extinction group appears to have received many more CSs. It would be interesting to determine whether the effect of cue extinction and instrumental extinction may summate to reflect the efficacy of instrumental-cue extinction when the cue extinction is yoked to the instrumental-cue extinction group.

In fact, there is some evidence to suggest that using a procedure of memory retrieval followed by cue extinction can indeed reduce relapse-like behaviour in a clinical setting (Xue *et al.*, 2012). Using this method detoxified human heroin addicts received 1 h heroin-associated cue extinction sessions daily for 2 days. When tested the next day, cue extinction sessions alone were ineffective in reducing cue-elicited blood pressure changes and self-reported craving for heroin. However, when a 5 min 'memory retrieval' session (exposure to heroin-associated cues) occurred 10 min prior to the cue extinction sessions, cue-elicited blood pressure changes and craving were significantly reduced, an effect that lasted at least 180 days following the last extinction treatment. This reduction in physiological response in combination with decreased craving might diminish the likelihood of relapse, which is often precipitated by these factors.

Such a cue retrieval-extinction procedure that reduces the cue-elicited emotion is based on the concept of 'reconsolidation'. Reconsolidation refers to the process of re-stabilizing a previously consolidated memory as it becomes temporarily vulnerable to disruption following retrieval (Misanin *et al.*, 1968; Nader *et al.*, 2000). In the study by Xue *et al.* (2012), retrieval-extinction may have decreased the motivational properties of heroin-related cues because extinction disrupted the reconsolidation of the retrieved drug-cue memory. Indeed, this has been previously demonstrated with a conditioned fear paradigm (Monfils *et al.*, 2009), and also with instrumental extinction of alcohol seeking (Millan *et al.*, 2013). It is widely accepted that retrieval-extinction is more effective because the destabilization process results in direct modification of the original memory (Hutton-Bedbrook and McNally, 2013), rather than formation of a new inhibitory memory, as is the case in normal extinction (Bouton, 2002). It is important to note, however, that Millan *et al.* (2013) actually report an increased motivation to consume alcohol

after retrieval-extinction compared with normal extinction. This finding indicates that the animal is not in fact returned to a naïve state, as would be the case if the original memory were disrupted (Hutton-Bedbrook and McNally, 2013). Furthermore, this explanation predicts that retrieval-extinction should only be effective when retrieval *precedes* extinction, and not vice versa, which has been demonstrated not to be the case (Baker *et al.*, 2013; Millan *et al.*, 2013). Therefore, although the retrieval-extinction paradigm represents an interesting non-pharmacological behavioural intervention for substance-abuse disorders, further research into the learning processes underlying this effect are certainly warranted.

Interestingly, there are several studies that examined the pharmacology underlying reconsolidation of drug-associated cue memories following self-administration (Lee *et al.*, 2005b; 2006; Wouda *et al.*, 2010; Milton and Everitt, 2012; Milton *et al.*, 2012). For example, infusion of antisense oligonucleotides to disrupt the expression of the immediate early gene *Zif268* into the basolateral amygdala immediately before retrieval of cocaine-associated cues can significantly reduce cue-induced reinstatement (Lee *et al.*, 2006). Further, systemic injection of the NMDA receptor antagonist MK-801 prior to retrieval of alcohol-associated cue memory can significantly disrupt subsequent conditioned approach, as well as PIT, of that same cue (Milton and Everitt, 2012; Milton *et al.*, 2012). In that study, the β-adrenoceptor antagonist propranolol had no effects, which appears inconsistent with a previous study that showed propranolol disrupted reconsolidation of alcohol-associated cue memory as measured by cue-induced reinstatement (Wouda *et al.*, 2010). It should be noted that Milton *et al.* (2012) used a single injection of propranolol whereas Wouda *et al.* (2010) used multiple injections over multiple retrieval sessions. Taken together, much more work is necessary to understand the pharmacology underlying reconsolidation, as well as extinction of drug-contingent cue memories; however, this area represents a promising avenue for the development of improvements to current treatments for substance-abuse disorders.

Cue extinction is context specific

Unfortunately, the clinical efficacy of CET is yet to be proven (Prisciandaro *et al.*, 2013; Unrod *et al.*, 2013; Yoon *et al.*, 2013), and a meta-analysis of all CET clinical trials up to 2002 did not show consistent evidence for the effectiveness of CET, with relapse rates for cue-exposure groups at equivalent levels as for control (Tiffany and Conklin, 2002). The reasons for the poor outcomes likely relate to the context specificity of extinction (Bouton, 2002). Specifically, extinction memory incorporates the context in which extinction is received, and removal from the extinction context tends to result in a retrieval of the original conditioned behaviour to a cue. This is the renewal effect discussed earlier (Bouton, 1988; 2002; Bouton and Swartzentruber, 1991). In fact, renewal has also been demonstrated in the human population. For instance, renewal has been reported in a study examining the behaviour of smokers (Thewissen *et al.*, 2006). Specifically, when a cue in one context signalled that participants could smoke, was then extinguished in an alternate setting, return to the original context resulted in an increase in craving elicited by the cue. Because CET usually occurs in a specific treatment setting, re-exposure to drug-taking contexts (which are usually many and varied) will result in renewal of cue-reactivity despite behavioural therapy. Therefore, reducing the context specificity of cue extinction represents an important area for further empirical investigation if treatment outcomes are to be improved.

A series of innovative experiments by Torregrossa *et al.* (2010, 2013) have provided insight into the neural circuitry underlying context specificity of cue extinction. In those studies, rats were first trained to lever press for cocaine that was paired with a light/tone discrete compound cue in a distinctive context, deemed context A. All rats then received instrumental extinction also in context A. In the initial study, rats then received cue extinction either in context A or a novel context B, or were merely placed in the novel context B without exposure to the discrete drug-associated cue (referred to as 'no cue extinction'; Torregrossa *et al.*, 2010). All rats were tested for cue-induced reinstatement in context A. Cue extinction in context A resulted in a decrease in cue-induced reinstatement when compared with the group that received no cue extinction. However, rats that received cue extinction in context B showed robust cue-induced reinstatement, at comparable levels with the no extinction group. This is consistent with the finding in human participants that when an alcohol-associated CS is extinguished in a different context to where alcohol was consumed, cue-elicited goal-directed behaviour is renewed upon return to the context where alcohol was given (Chaudhri *et al.*, 2008). The procedure used by Torregrossa *et al.* (2010, 2013) therefore provides an excellent preclinical model to investigate why CET may be less effective in controlling drug seeking in contexts beyond the therapist's office (Conklin and Tiffany, 2002).

The context specificity of cue extinction appears to be mediated by NMDA receptors in the NAc. Either systemic or intra-NAc core injection of the NMDA receptor partial agonist D-cycloserine (DCS) prior to the cue extinction session in context B significantly reduced cue-induced reinstatement in context A compared with saline (Torregrossa *et al.*, 2010). By comparison, DCS failed to have any effects when infused into the lateral amygdala, medial prefrontal cortex subregions or dorsal hippocampus. Importantly, systemic DCS injection prior to cue extinction in context A had no effect on subsequent reinstatement in context A. These findings indicate that NMDA receptor signalling specifically in the NAc core is important either for facilitating cue extinction memory to make it more generalizable across contexts, or for contextual encoding during cue extinction to make it context-independent. These hypotheses were tested in a subsequent study that showed that decreasing NMDA receptor signalling in the NAc core by the NMDA receptor antagonist D-AP5 prior to cue extinction in context B increased conditioned reinforcement for the same cue in context B without affecting responding in context A (Torregrossa *et al.*, 2013). This suggests that that down-regulation of NMDA receptor activity during cue extinction resulted in attenuated cue extinction, so the cue maintained its motivational properties. On the other hand, inactivation of the ACC using a cocktail of $GABA_{A/B}$ receptor agonists (muscimol/baclofen) immediately prior to cue-extinction session in context B resulted in a decrease in reinstatement when the animals were returned to context A. Taken together, these results indicate that while NMDA signalling in NAc core is important for the strength of

cue extinction memory, ACC is important for the contextual information that is encoded during cue extinction. Although the neurobiological mechanisms underlying cue–context interactions are yet to be fully delineated, these results provide a strong foundation for further research into the precise neurobiology of cue extinction.

Importantly, studies employing animal models suggest that cue-exposure therapy in behaviourally relevant settings may be a promising endeavour in terms of translational value (Conklin and Tiffany, 2002; Conklin *et al*., 2010). The use of virtual reality technology, may be an effective tool for this type of therapy, as it minimizes the obvious logistical issues related to real-world context-specific treatment (Kuntze *et al*., 2001; Culbertson *et al*., 2010; García-Rodríguez *et al*., 2012; Ferrer-García *et al*., 2013; Yoon *et al*., 2013). In fact, extinguishing cues in varied contexts may prove especially beneficial for relapse outcomes, as renewal of cue-induced drug seeking has been found to decrease following extinction in multiple contexts (Chaudhri *et al*., 2008). However, to date, this approach has been less successful in clinical trials (Tucker *et al*., 2008). It may be the case that in humans, the many complex factors involved in a context (e.g. the stimuli involved with being in a bar surrounded by friends) may be more powerful compared with relatively simple discrete cues (e.g. glass filled with beer) in initiating drug seeking (Bouton, 2002).

Contextual cue extinction can reduce relapse

In light of this, it may be more useful for extinction-based therapy to also incorporate contextual drug-associated cues in addition to discrete cues. In fact, Pearce and Hall (1979) showed that two exposure sessions to a context previously associated with instrumental responses for food were enough to significantly reduce food-seeking behaviour in subsequent sessions, compared with the non-exposed control group, even in the absence of any instrumental extinction. It appears that reward-seeking behaviour was reduced because of extinction of context–reinforcer associations. This phenomenon of contextual cue extinction has only recently been extended to a model of substance abuse using a drug reinforcer rather than a natural reward. Following cocaine self-administration, Ghasemzadeh *et al*. (2009a,b; 2011) gave rats either instrumental extinction, exposure to the self-administration chambers (context extinction) or left them in their home cages. In subsequent extinction tests, while context extinction was less effective at reducing responding compared with instrumental extinction, rats that received context-exposure alone gave fewer cocaine-seeking responses than those in the home cage condition. Consistent with this, Kim and colleagues (2014) recently showed that daily context extinction over 9 days was in fact equally as effective as daily instrumental extinction in reducing cocaine-primed reinstatement, compared with abstinence.

Conversely, Buffalari *et al*. (2013) failed to see a significant reduction of discrete cue-induced reinstatement following context extinction in the absence of instrumental extinction. However, there were several critical differences between these studies. Firstly, Buffalari *et al*. (2013) had no control group that did not receive any context extinction, providing no comparison for the effect of context extinction on reinstatement. Furthermore, in Buffalari *et al*. (2013), lever pressing was paired with a light/tone compound cue and at reinstatement, presentation of the discrete cue was contingent on lever pressing. Therefore, high levels of reinstatement may actually reflect responding for the conditioned reinforcer rather than a failure of context extinction *per se*. By comparison, in Kim *et al*. (2014), cocaine delivery during self-administration was not paired with any contingent cue and reinstatement was triggered by a priming injection of cocaine. That is, drug experience was never associated with a discrete cue. Critically, it has been suggested that the drug-taking context can act indirectly as an 'occasion setter' in situations where associations with drug taking are ambiguous (Holland, 1992). By the same token, the presence of discrete, response-contingent cues at reinstatement in Buffalari *et al*. (2013) may have provided a disambiguating signal for drug availability. This could have overpowered potential contextual influences, masking any possible effects of context extinction. Overall, extinction of contextual cues as well as discrete cues presents a promising area for further research, with strong translational application.

Concluding remarks

As drug experience is inevitably associated with cues in the human scenario, research aimed at examining the role of environmental cues in drug-seeking behaviour is critical for understandings of substance abuse. The self-administration reinstatement model is a valuable tool for investigating how these stimuli mediate drug seeking, and for understanding the neurobiology underpinning in this behaviour. Studies using variations on this procedure have revealed that discrete, discriminative and contextual drug-associated cues can guide drug seeking via both conditioned reinforcing and incentive motivational properties gained via association with drugs of abuse. It is well documented that these stimuli are able to elicit craving and withdrawal symptoms in human drug abusers, as well as contributing to relapse episodes. Critically, relapse to substance use remains one of the most difficult hurdles to overcome in the treatment of substance-abuse disorders. Therefore, animal studies that incorporate drug-associated environmental stimuli have strong translational value for improving treatment outcomes.

In particular, the extinction of cues associated with drug use represents an important area for empirical investigation using animal models. Despite cue extinction constituting a more viable method for inhibiting drug-seeking behaviour than instrumental extinction, literature specifically on drug-associated cue extinction is scarce. What is more, the meta-analysis of results from clinical trials revealed that CET is not particularly effective in reducing relapse in the human population (Tiffany and Conklin, 2002). One of the reasons for this, as demonstrated by animal research, is that extinction is context specific (Bouton, 2002). However, emerging behavioural evidence indicates that cue extinction may in fact be able to reduce cue-induced relapse if the problem of generalizability can overcome. Further studies using models of discrete and contextual cue extinction are therefore essential for the development of improved cue–extinction-based treatment. Ultimately, it is the contribution of laboratory animals

that will enhance the lives of patients in the community living with substance-abuse disorders.

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Conflict of interest

None.

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