Skewed by Cues? The Motivational Role of Audiovisual Stimuli in Modelling Substance Use and Gambling Disorders

Michael M. Barrus, Mariya Cherkasova and Catharine A. Winstanley

Abstract The similarity between gambling disorder (GD) and drug addiction has recently been recognized at the diagnostic level. Understanding the core cognitive processes involved in these addiction disorders, and in turn their neurobiological mechanisms, remains a research priority due to the enormous benefits such knowledge would have in enabling effective treatment design. Animal models can be highly informative in this regard. Although numerous rodent behavioural paradigms that capture different facets of gambling-like behaviour have recently been developed, the motivational power of cues in biasing individuals towards risky choice has so far received little attention despite the central role played by drug-paired cues in successful laboratory models of chemical dependency. Here, we review some of the comparatively simple paradigms in which reward-paired cues are known to modulate behaviour in rodents, such as sign-tracking, Pavlovian-to-instrumental transfer and conditioned reinforcement. Such processes are thought to play an important role in mediating responding for drug reward, and the need for future studies to address whether similar processes contribute to cue-driven risky choice is highlighted.

Keywords Decision making · Cues · Dopamine · Gambling · Animal models

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1 Introduction

Gambling is a common recreational pastime that can lead to debilitating and compulsive behaviour for some users. While most individuals are able to gamble within reasonable limits, some 12.5 % of the general public demonstrates subclinical problem gambling, and 2.5 % meet the criteria for gambling disorder (GD), a Diagnostic and Statistical Manual, Fifth Edition (DSM-V) recognized behavioural addiction characterized by a loss of control over gambling (Cunningham-Williams et al. 2005). Despite GD's prevalence and social and individual costs, the neurobiology of gambling behaviour is not well understood. This lack of insight has thus far limited treatment of the disorder (Williams et al. 2008). Laboratory-based models of gambling behaviour are thus extremely useful in that they allow researchers to isolate the cognitive and neurobiological processes implicated in gambling. Analogues of these paradigms with strong face, construct and predictive validity can then be designed for use with non-human laboratory animals, thereby enabling the causative nature of particular brain areas or neurotransmitter systems in maladaptive gambling behaviour to be determined (see Potenza 2009; Cocker and Winstanley 2015 for discussion). Establishing such robust models has the potential to catalyse the development of pharmacological treatments for GD, as well as inform our understanding of the very nature of GD and therefore remains an important research priority in the field.

Perhaps the most widely used cognitive task that assesses decision-making processes similar to those recruited during gambling behaviour is the Iowa Gambling Task (IGT) which provides a reliable measure of preference for risky (disadvantageous) over conservative (advantageous) options (Bechara et al. 1994). Although ostensibly designed to capture "real-world" decision-making in which all

options could lead to both gains and losses according to initially ambiguous odds, it has been used as a proxy for gambling largely due to its strong superficial resemblance to the act of gambling. In the IGT, human participants must choose between decks of cards, each of which is associated with different schedules of risk and reward, in order to maximize the amount of money or points earned. Two of the decks (decks A and B) are associated with sizeable wins but also disproportionately larger losses, leading to a net loss over time. The remaining two decks (decks C and D) are associated with smaller wins but also smaller losses, and exclusive choice of these decks leads to a net gain over time. Subjects must learn to resist choosing the superficially tempting options (A and B) in order to succeed at the task, and work with the IGT has demonstrated impairment in a number of clinical populations including pathological gamblers (Goudriaan et al. 2005; Shurman et al. 2005; Verdejo-Garcia et al. 2007a, b). While there are numerous aspects of problematic gambling behaviour that are not captured by this task (see Cocker and Winstanley 2015 for discussion), there is no doubt that work with the IGT has made a significant contribution to our understanding of decision-making under conditions of risk and ambiguity. Understandably, developing rodent analogues of the IGT was considered by many researchers a logical first-step in generating a model of gambling behaviour that would hopefully prove useful in capturing elements of disordered gambling and identifying viable pharmacotherapeutic targets (de Visser et al. 2011).

One such model is the rat Gambling Task (rGT), in which animals are allowed to choose between four options, signalled by illumination of four response apertures, loosely analogous to the four decks of cards used in the IGT in that each is associated with unique schedules of food reward or "timeout" punishment (Fig. 1; Zeeb et al. 2009). As is true of the IGT, the best strategy on this task is to favour options associated with smaller rewards but also smaller punishments—this more conservative approach leads to the steady accumulation of the greatest amount of reward over time. In contrast, a preference for these tempting "high-risk high-reward" outcomes is ultimately disadvantageous: although such options can yield greater rewards per trial, the disproportionately larger punishments result in considerably less benefit during the course of a session. Critically, this task incorporates loss, a central component of naturalistic gambling paradigms, through the use of punishing timeout periods. Given the limited length of each session, time is a resource animals are at risk of losing if their wager is unsuccessful. In essence, the disadvantageous options and their longer timeout periods require animals to balance the desire for larger rewards with the risk of the loss of future earning potential. Most rats acquire the optimal strategy readily, and such decision-making appears to depend on similar neural circuitry as is implicated in performance of the IGT (Zeeb and Winstanley 2011, 2013; Paine et al. 2013; Zeeb et al. 2015).

While this task, and others, provides valuable insight into gambling-like behaviours, there are elements of real-world gambling that have not yet been addressed by animal models. To our knowledge, little work has been done evaluating the role of salient cues in modulating decision-making. This is a potentially rich area of research; real-world gambling is rife with salient cues, and their influence on

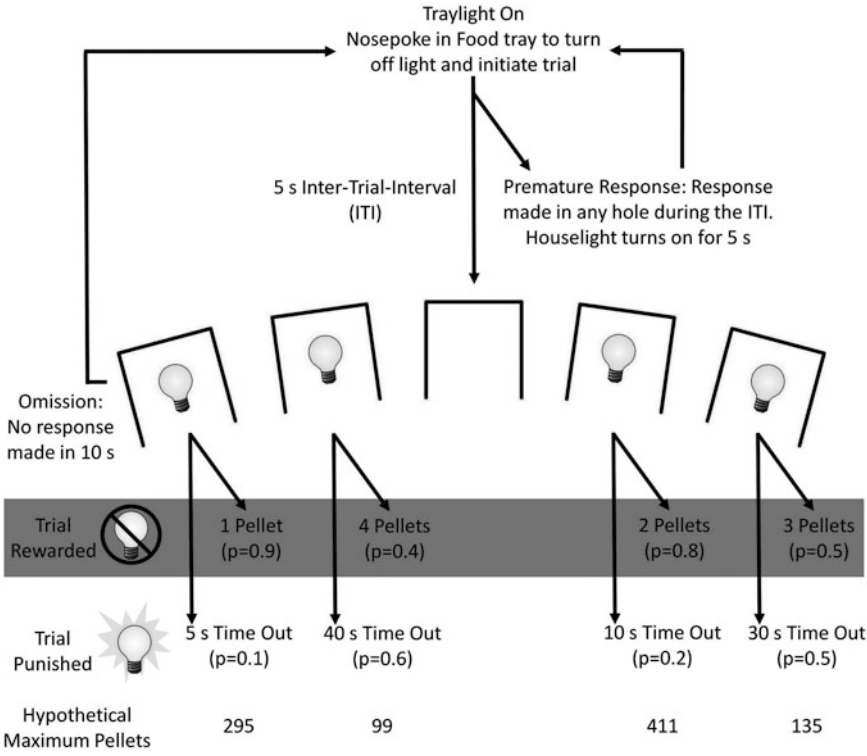

Fig. 1 Task schematic of the rat Gambling Task (*rGT*). Each trial begins with the illumination of the tray light. A nosepoke in the tray extinguishes the tray light and initiates a 5-s inter-trial interval (*ITI*), during which all lights in the chamber are off. Following the ITI, stimulus lights are illuminated in apertures 1, 2, 4 and 5, each of which has a different schedule of reward/punishment associated with it. If the animal nosepokes one of the apertures within 10 s, the animal is rewarded or punished according to the schedule associated with that aperture. The size of reward and duration of punishment for each option are indicated on the schematic; the *p*-value in brackets beneath each of those indicates the probability of a win or loss on any given trial. On a rewarded trial, the tray light is illuminated and the requisite pellets dispensed. A response at the tray then initiates a new trial. On a punished trial, the light in the chosen aperture flashes at a frequency of 0.5 Hz for the duration of the timeout period; all other lights are extinguished. At the end of the timeout, the tray light is once again illuminated and the animal can initiate a new trial. A nosepoke at an aperture during the ITI is scored as a premature response and initiates a 5-s timeout period during which the houselight is illuminated. Failure to make a response at an aperture within 10 s of the stimulus lights being illuminated is scored as an omission; the stimulus lights are extinguished, the tray light once again illuminated, and the animal is able to initiate a new trial. Adapted from Zeeb et al. (2009)

gambling behaviour may be significant. Experimental work with human subjects has demonstrated that manipulating the gambling environment can affect gambling behaviours (Brevers et al. 2015), and some have proposed that attentional biases towards salient cues may underlie the transition from recreational to problem gambling (Grant and Bowling 2014). The influence of salient cues on decision-making is

not limited to gambling; the ability of drug-related stimuli to promote craving and relapse is well documented and represents one of the most destructive forms of cue-biased behaviour (Childress et al. 1992; Grimm et al. 2001; Shaham et al. 2003). Being able to demonstrate cue-induced maladaptive decision-making in animal models would be of value to both gambling and substance abuse research and could more generally aid in the characterization of how salient cues exert their effects on decision-making. We will first consider the ways in which the study of conditioned cues has influenced models of addiction.

2 The Impact of Conditioned Cues in Models of Drug Addiction

2.1 Pavlovian Conditioning and Drug Addiction

It is necessary to define the term "cue" as we will be using it before embarking on a discussion of the cues' significance and contributions to decision-making. In the light of the focus of this review on the motivational impact of cues, any stimuli that have come to be associated with reinforcement satisfy the definition. As such, our discussion of cues must essentially begin with classical conditioning, famously laid out by Ivan Pavlov following his discovery of the motivational power of a bell. Originally intending to study the role of salivation in digestion, Pavlov noticed that his canine subjects began to salivate upon exposure to the experimenter who regularly distributed meat powder (Pavlov 1927). Pavlov then paired a ringing bell with the distribution of meat powder and found, with time, that the bell alone was sufficient to evoke salivation in his animals. The bell therefore became what is termed a conditioned stimulus (CS) capable of eliciting a conditioned response (CR) as if it were the primary reward itself.

The real-world examples of this interaction are myriad, and research on the subject has placed particular emphasis on understanding the prominent role of drug-related cues in addiction and substance abuse (Childress et al. 1993). Drug-related cues can be anything the user associates with the drug-taking experience, be that individuals with whom the user takes drugs, locations in which the user commonly takes drugs or drug-associated paraphernalia such as pipes or syringes. After repeated pairings of these people, places and things with the drug-taking experience, these formerly neutral stimuli come to predict the delivery of reward and may even take on the motivational properties of the reward, promoting drug-seeking behaviour and CRs. Drug-associated cues such as paraphernalia and location can induce powerful craving and arousal states (Childress et al. 1993); exposure to smoking-related cues increases subjective craving for cigarettes (Carter and Tiffany 1999b), while exposure to alcohol-related cues increases subjective craving for alcohol (Schulze and Jones 1999). The degree of attentional bias towards these cues can distinguish between abusers and non-abusers/non-users, and

among users, substance-related attentional bias tends to be positively related to the quantity and frequency of use, though this relationship has been less consistent for smokers (Robbins and Ehrman 2004; Cox et al. 2006).

While Pavlovian associations between drug-related stimuli and consumption are believed to contribute to compulsive drug use, this simple form of associative learning is unlikely to be the sole mechanism mediating behaviour. Were these simple stimulus–stimulus pairings, the CSs should produce effects that mimic either the appetitive, intoxication-like effects the substance produces or the aversive, withdrawal-like effects associated with physical withdrawal from the substance. While drug-paired cues can promote withdrawal-like experiences in some circumstances (Carter and Tiffany 1999a), these effects do not appear to be consistent. Instead, cues more readily produce increases in subjective craving and physiological arousal as described previously (Carter and Tiffany 1999b). Given that these are not the unconditioned responses evoked by the substance but instead appetitive behaviours directed towards the substance, it suggests that the affective properties of cues are more complex than a simple Pavlovian model can account for. Several compelling theories have been proposed to explain these effects.

2.2 *The Incentive Sensitization Theory of Drug Addiction*

One of the most prominent of these is the theory of incentive sensitization (Robinson and Berridge 1993), which proposes an elegant mechanistic explanation of the neurobiological mechanisms underlying the ability of cues to guide behaviour. Reward-paired cues can acquire incentive salience, i.e. motivational significance, through mesocorticolimbic dopamine signalling (Berridge and Robinson 1998). Repeated use of drugs of abuse can lead to the sensitization of dopaminergic systems related to reward, motivation and salience attribution. This "incentive sensitization" results in heightened sensitivity to drug-related stimuli, which increases subjective motivation (or "wanting") for drugs of abuse. Continued substance use can result in long-lasting "hypersensitivity to the incentive motivational effects of drugs and drug-associated stimuli" (Robinson and Berridge 1993), with dopamine mediating the "wanting" component. Reward-related cues themselves become "wanted" or motivationally salient and capable of driving behaviour to a greater extent than reward alone could (Heinz et al. 2004). The misattributions of salience to drug-related cues can lead to significant behavioural changes that long outlast physical dependence, while also providing a better explanation for complex patterns of drug-seeking behaviour seen in substance dependence than simple Pavlovian paradigms of stimulus–stimulus learning. In essence, the CS becomes an "incentive stimulus", capable of influencing action selection and goal-directed behaviour (Saunders and Robinson 2010; Yager and Robinson 2013).

Although the theoretical basis for the incentive salience model of addiction was elucidated using laboratory animals, considerable evidence points to the motivational significance of cues in human-addicted populations. Several studies have

reported increases in self-reported liking for drug-paired locations following conditioning (Childs and de Wit 2009, 2013), and smokers preferred to listen to a smoking-paired cue over a control cue (Mucha et al. 1998). Furthermore, the interoceptive cues triggered by smoke inhalation have been found to significantly contribute to the desire to smoke, beyond the simple administration of the addictive chemical nicotine (Naqvi and Bechara 2005, 2006). An instrumentally conditioned cue that resulted in the opportunity to smoke produced greater attentional bias than a control cue did (Hogarth et al. 2003). Furthermore, previously cocaine-paired cues sustained responding in cocaine-dependent subjects, even though self-reports indicated that subjects were aware they were no longer receiving cocaine (Panlilio et al. 2005). Collectively, these results suggest that drug-paired cues become motivationally "wanted" following conditioning, consistent with the incentive sensitization model. In addition, both behavioural and dopamine drug sensitizations have now been demonstrated in humans (Boileau et al. 2006; O'Daly et al. 2011). Though the findings have not been entirely consistent, this could be in part explained in by the presence versus absence of drug-paired contextual cues, which appear to be critical for expression of sensitization (Leyton and Vezina 2013, 2014).

2.3 Attentional Bias in Drug Addiction

Other theories have expanded upon the contingencies necessary for cues to exert their effects. Field and Cox suggested that existing theories were incomplete, specifically arguing the motivational power of drug-related cues is contingent on the availability of the drug (Field and Cox 2008). In this model, drug-related cues come to gain significance not simply because of recurrent pairing with the substance but because these cues signify drug availability. It is this expectancy of drug availability then that elicits CRs such as subjective craving and attentional bias towards drug-paired cues. Therefore, cognitive appraisal of the availability of the substance is an important mediator of the ability of salient cues to promote conditioned responding. The difference between this and incentive salience is subtle, but it has some support in research demonstrating that smokers report greater cravings for cigarettes when there is some possibility of smoking as compared to no possibility to do so (Bailey et al. 2010). Furthermore, smoking-paired CSs have been shown to evoke craving only when subjects have an imminent opportunity to smoke (Dar et al. 2010). However, to the best of our knowledge, these effects have been difficult to replicate with non-tobacco substances such as alcohol (Davidson et al. 2003; MacKillop and Lisman 2005), suggesting the theory is imperfect. Nonetheless, it presents a compelling demonstration that at least in some cases the motivational force of CSs may be contingent on a variety of complex environmental factors.

3 The Role of Cues in Gambling

While the above theories are framed within the context of substance abuse, the powerful motivational effects of cues are not limited to drug-taking and extend to behavioural addictions and gambling in particular. The effects of gambling-associated cues in problem gamblers are comparable to the effects of drug cues in problem users in at least some ways. Exposure to gambling cues can induce craving in problem and frequent gamblers (Kushner et al. 2008; McGrath et al. 2013). Problem gamblers also appear to be more sensitive to such cues than non-problem gamblers. Adolescent pathological gamblers reported being more attracted by music, lights and noises produced by slot machines than non-pathological adolescent gamblers (Griffiths 1990). Removing sound from video lottery terminals and decreasing speed of play decreased ratings of enjoyment, excitement and tension-relief more in pathological than in non-pathological gamblers (Loba et al. 2001); pathological gamblers also experienced more difficulty stopping play in the presence of sound cues and at higher play speeds. Though it is not possible here to disentangle the effect of sound alone on gambling behaviour from the concurrent changes in rate of play, it at least suggests that sound can modulate the experience of gambling for individuals who exhibit disordered gambling. Furthermore, like problem substance users, problem gamblers show attentional biases towards gambling-related stimuli across different paradigms, including gambling Stroop, dual tasks, flicker and attentional blink tasks, as well as eye fixation and ERP reactivity measures though the findings have not been entirely consistent (for review, see Honsi et al. 2013). Attentional bias towards gambling cues has been suggested to play a critical role in the transition from recreational to problem gambling (van Holst et al. 2012; Grant and Bowling 2014).

Despite these similarities, there may also be important differences in the roles that cues play in substance versus gambling contexts. Similar to drug cues, gambling cues are associated with rewards (in this case, monetary), or the possibility of rewards. However, in the case of gambling cues are linked with rewards at multiple levels. Broad contextual cues, such as red lights, casino sounds and appearance of gambling tables and machines, are not specifically associated with outcomes, yet signal the possibility of a reward if gambling is initiated. These seem phenomenologically most similar to drug cues. Anticipatory cues, such as reel spins and accompanying music, signal the possibility of an imminent reward in a given play. Outcome-specific cues, such as flashing lights and sounds of tumbling coins of the slot machine when a win occurs, are concurrent with and symbolic of monetary rewards and hence might themselves help reinforce and maintain gambling once it has already been initiated. Whereas other research has posited that sound serves as an occasion setter or discriminative stimuli that essentially sets the stage for other stimuli to modulate gambling behaviour (Griffiths and Parke 2005), some have suggested that win-associated cues are second-order conditioned stimuli, which become rewarding in their own right (Dixon et al. 2014) (see below for discussion of conditioned reinforcement). This distinction is subtle but important. Again, describing salient cues such as win-related lights and sounds as mere occasion-setters relegates them to

a supporting role in maintaining disadvantageous behaviour, rather than a driving force with direct influence on decision-making. They have frequently been described as the former; lights and sounds of fruit machines have been characterized as "psycho-structural… characteristics" that serve as "gambling inducers" (Griffiths 1993), serving to "create an atmosphere which is probably conducive to gambling" (Caldwell 1974). In contrast, Dixon et al.'s work regards gambling-related stimuli as having a function similar to that of drug-related CSs, in that sound is capably of directly influencing disadvantageous gambling behaviour.

Different types of gambling cues (contextual, anticipatory, outcome-specific) may influence the gambler's experiences and behaviour in different ways—a possibility that has not yet been comprehensively studied, but appears to be supported by at least some evidence. Though this research is in its infancy, the handful of existing studies suggest that contextual gambling cues affect subjective experiences and energize behaviour of the player, whereas outcome-specific (win-associated) cues additionally affect and distort gambling-related cognitions. Thus, ambient cues (red lights, casino sounds) that were not specifically associated with outcomes on the IGT had a positive effect on mood and speeded up reaction times to make choices following losses, but had no effect on choice behaviour (Brevers et al. 2015). Higher tempo of background music increased the speed of betting in a virtual roulette game, especially when combined with ambient red light, but did not affect bet size or the amount spent (Dixon et al. 2007). Though the effects of anticipatory gambling cues remain mostly unstudied, one experiment found that that sequential presentation of symbols on the different reels may be more reinforcing to the players than simultaneous presentation of the symbols on all the reels, as sequential presentation increased the number of games played (Ladouceur and Sevigny 2002); however, varying the duration of the reel spin did not affect any aspect of gambling behaviour (Sharpe et al. 2005).

Unlike contextual cues, outcome-specific cues appear to affect play-related cognitions. The presence versus absence of specifically win-associated auditory cues —jingles varying in length and intensity as a function of win size—not only resulted in increased arousal (measured via galvanic skin responses and self-report) and higher preference ratings for the cued version of the task, but also led the subjects to overestimate their frequency of winning (Dixon et al. 2014). Other evidence comes from studies of win-associated audiovisual cues that slot machines commonly present during "wins" that actually fall short of the amount wagered—in other words "losses disguised as wins" (LDW) (Dixon et al. 2010, 2015). Such audiovisual "disguise" proves compelling: LDWs resulted in indices of physiological arousal that were more similar to those produced by genuine wins than those produced by frank losses. Sounds accompanying LDWs, in their own right, had a significant impact on subjects' impression of winning or losing: when LDWs were accompanied by winning sounds, players miscategorized the majority of these trials as wins and overestimated their overall frequency of winning; when LDWs were accompanied by losing sounds, both categorization and recall of winning frequency were considerably more accurate. Gambling-related cognitive distortions are believed to play an important role in driving pathological gambling (Clark 2010). Therefore, the

demonstrated effects of outcome-specific cues on cognitive variables raise the possibility that these cues could thereby help drive disadvantageous gambling-related choices and behaviour. To the best of our knowledge, this possibility has not yet been tested in humans, and the effects of outcome-associated cues on human choice behaviour remain unstudied. This area deserves more attention. Research with both human and animal models with careful manipulation of cues at every level would provide valuable insight that could ultimately inform prevention and treatment of disordered gambling. Further, given the sophistication of cues in gambling and gaming, systematic study of these cues and their effects could produce new insights regarding the role of cues in addiction more generally, which may have escaped recognition with the focus on the apparently simpler drug cues.

3.1 Animal Models of the Influence CS Exert over Behaviour

While the value of human gambling research is self-apparent, the use of animal models provides insight that complements and expands on the human literature. Examining the behavioural influence of cues in rodent models provides more explicit neurobiological information and allows for manipulations that are not possible in human subjects. While the research into gambling-specific effects of cues is more limited (if not non-existent) in animal models, several established animal paradigms do investigate the ability of CSs to affect behaviour.

3.2 Sign-Tracking

Pavlov's seminal research demonstrated that some animals began to treat the stimuli predictive of reward as though it were the reward itself (Fig. 2). He wrote "…the animal may lick the electric lamp (that is predictive of food), or appear to take the air into its mouth, or to eat the sound, licking his lips and making the noise of chewing with his teeth as though it were a matter of having the food itself" (Pavlov 1927). Approach to and engagement with the cue suggested that it had taken on motivational properties of its own, and was not merely predictive of reward for some animals but rewarding in and of itself. This sort of engagement with the CS has been well documented in the literature; pigeons will peck at a cue light that predicts reward delivery, even though food delivery is not contingent on any instrumental response (Brown and Jenkins 1968), while raccoons trained to deposit a token to receive a food reward treat the token as though it were food itself, washing it and gnawing on it for extended periods of time despite the fact that these behaviours prevent the acquisition of the food itself (Breland and Breland 1961). In each of these

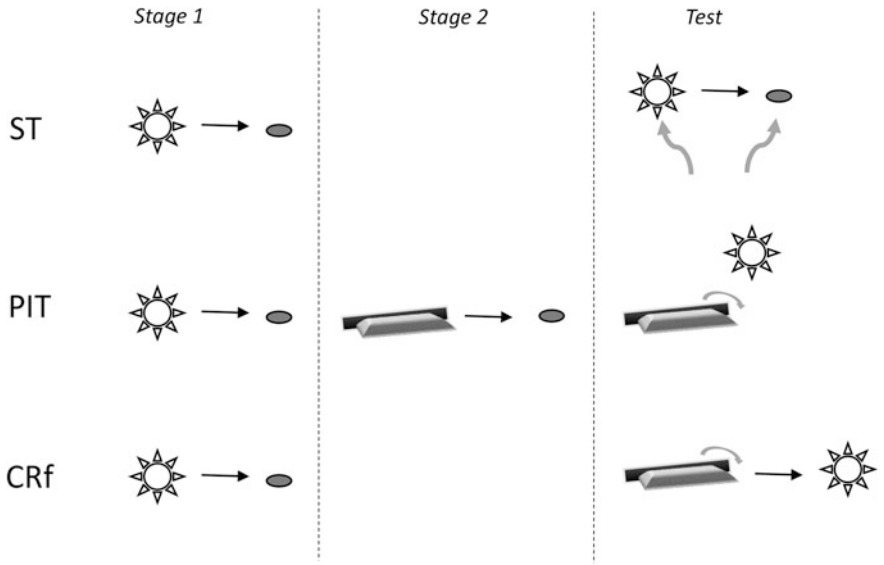

Fig. 2 Simplified illustration of the training stages need for sign-tracking (*ST*), Pavlovian-to-instrumental transfer (*PIT*) and conditioned reinforcement (*CRf*). *Black arrows* represent contingencies in place. *Grey arrows* represent the animal's behaviour. The first training stage for all three processes is identical: the animal learns that a conditioned stimulus (*CS*) is associated with an unconditioned stimulus (*US*), such as reward delivery, through classical conditioning. The CS is represented here as a visual stimulus for ease, but can theoretically be a cue of any modality. The US is depicted as a sugar pellet, but can likewise be any US. During the sign-tracking procedure, either in a designated test session or throughout acquisition, the experimenter then measures the number of times the animal approaches or interacts with the CS (sign-tracking), or instead approaches or interacts with the site of reward delivery (goal-tracking). During PIT, the animal learns that an operant response, such as depressing a lever as shown here, leads to delivery of reward. In this depiction, the reward is identical to that used in the classical conditioning session as for outcome-specific PIT, but could also be a reward of similar valence but different quality as in general PIT. In the critical test session, the animal makes the operant response in extinction, and the CS is presented non-contingently. Successful PIT is indicated by elevated responding during the CS. To test for CRf, the degree to which the animal must make a novel operant response, reinforced solely by delivery of the CS, is determined. For all three paradigms, an additional CS is typically also included, presentation of which does not have any consequences, to control for non-specific responding for cues (omitted from the figure for clarity)

examples, it appears that the reward-predictive cue acquired great incentive value of their own, sufficient to distract at least some of the animals from the US.

Engagement with reward-predictive cues has come to be known as sign-tracking (as opposed to goal-tracking, or engagement with the reward itself), and the study of this phenomenon has provided some of the most robust evidence for the incentive sensitization model of addiction described above. In one well-documented model of sign-tracking (ST, Robinson and Flagel 2009) (see chapters by Robinson et al. and Meyer et al., in this volume), a lever with an illuminated light above it is presented for a brief period of time. It is retracted, and a reward pellet is delivered to

a food magazine immediately proximate to the lever. Importantly, the delivery of the reward pellet is not contingent on any instrumental response from the subject. Animals trained on this task can be divided into three groups based on their behavioural response to the illuminated lever. One group (the goal-trackers) orients towards the food magazine when the lever is illuminated, while another group (sign-trackers) engages with the lever itself. A third group spends approximately the same time with both the illuminated lever and the food magazine. Researchers have posited that the inclination to approach the reward-associated cue or "sign" over the reward itself represents a misattribution of salience that may be a marker for vulnerability to a host of behavioural disorders, including addiction (Robinson and Flagel 2009). In essence, the task provides a measure of the ability of salient reward-related cues to gain control over behaviour, roughly analogous to processes seen in the maintenance and reinstatement of drug addiction. Work with the task has demonstrated, among other findings, increased sensitivity to cocaine-induced plasticity in sign-trackers (Flagel et al. 2008), distinct alterations in the dopamine system in sign-trackers and goal-trackers (Flagel et al. 2007) and elevated corticosterone in sign-trackers relative to other groups (Tomie et al. 2000, 2004). ST also seems to be associated with other traits thought to confer vulnerability to addiction, including high reactivity to a novel environment (as measured by locomotor activity) (Flagel et al. 2010) and increased reinstatement of drug-seeking following extinction of cocaine self-administration (Saunders and Robinson 2010). ST thus has advantages in examining specific addiction-related behavioural profiles, and work with the model is providing valuable insights into individual attributions of incentive salience and the "misbehaviour of organisms", to borrow Breland's phrasing (Breland and Breland 1961).

3.3 Pavlovian-to-Instrumental Transfer

Pavlovian-to-Instrumental Transfer (PIT) examines the ability of CSs associated with an outcome to invigorate instrumental responding for either the same outcome (outcome-specific PIT), or one of a similar valence (appetitive or aversive), even when there is no formal association between CS and instrumental responding (see chapter by Corbit and Balleine in this volume). In outcome-specific PIT procedures, subjects learn two distinct contingencies. The first is a simple classical conditioning procedure in which the non-contingent delivery of a reinforcer is paired with a stimulus. Importantly, reinforcement is not dependent on any response from the subject. The second is an instrumental responding procedure where the subject must execute some behaviour in order to receive the same reinforcer (i.e. there is a causal relationship between the animal's behaviour and the delivery of reward). The testing period then takes place in extinction conditions, where the instrumental response is not rewarded, in order to see whether presentation of the reward-paired stimuli invigorates engagement in the previously reward-paired action.

The ability of CSs to encourage responding for an US in PIT paradigms probably reflects the CSs' ability to increase motivation (either generally or more specifically) for the reinforcer used. An alternative interpretation that deserves consideration is whether PIT instead reflects any crossover between the instrumental response and some behaviour evoked by the CS. For example, a CS can prompt subjects to approach the location of reward (Brown and Jenkins 1968), and if the instrumental response must be made proximally to the site of reinforcement, the effects of the CS on instrumental responding might merely be an interaction between responses to the CS and the particular instrumental behaviour. While there may well be something to this theory (Karpicke et al. 1977), PIT is not reducible to this mere interference effect. Lovibond conditioned a jaw-movement response to a CS in rabbits by pairing it with the administration of a sucrose solution, and then separately trained these same subjects to press a lever for the sucrose solution (Lovibond 1983). When the CS was presented while the subjects were working for reward, it invigorated lever-pressing. This suggests the CS evoked a general increase in motivation, as the jaw-movement CR did not promote anything resembling lever-pressing and in fact reduced lever-pressing when evoked by sucrose administration. Furthermore, the expression of PIT critically depends on the motivational state of the animal; in order for food-paired cues to evoke PIT, the animal must be hungry during the test phase (see Cardinal et al. 2002 for further discussion). PIT therefore appears to provide reliable evidence that CSs can produce a general increase in motivation for desirable USs, suggesting one method by which cues can come to influence behaviour. This phenomenon has also recently been described in human subjects, and stronger PIT observed in individuals that exhibit greater sign-tracking to a reward-paired cue (Garofalo and di Pellegrino 2015).

3.4 Conditioned Reinforcement

Tests of conditioned reinforcement (CRf) may look methodologically quite similar to PIT- again, the CS is first classically conditioned to reward delivery. However, the subsequent CRf test then determines the degree to which rats will perform a novel response, such as lever-pressing, that is reinforced solely by the CS. Thus, in contrast to PIT, presentation of the CS is *entirely contingent* on the animals' behaviour (Robbins 1978; Williams 1994). The process of CRf is thought to underlie second-order schedules of reinforcement of drug self-administration that are typically used to assess drug-seeking rather independent of drug-taking (Arroyo et al. 1998; Di Ciano and Everitt 2005). In such paradigms, animals initially make a single response to receive an infusion of an addictive substance, such as cocaine, paired with an audiovisual CS, such as a light or tone. Over successive iterations, an association is therefore formed between experience of the drug and the CS. The power of this association is so strong that this CS is then capable of supporting operant behaviour independent of drug delivery, as demonstrated in subsequent

training sessions in which the response requirements are progressively increased such that animals must respond numerous times to receive presentation of the CS, and numerous CSs prior to receipt of a single drug infusion. Similar findings have been reported in humans (Panlilio et al. 2005). Such second-order schedules allow for the extensive study of the neurobiology underlying responding for drug in the absence of any confounding behavioural effects caused by drug delivery.

3.5 Interim Summary

All three processes, ST, PIT, and CRf, can be considered somewhat hierarchically in that the property of cues which they measure increases in behavioural significance, from attracting interest (ST), to influencing ongoing goal-directed behaviour (PIT), and finally to becoming the goal itself (CRf). All of these cue-driven processes have also been implicated in addiction, but in subtly different ways. As discussed above, ST is thought to reflect the degree to which cues paired with addictive drugs can induce the desire to use (Flagel et al. 2009). PIT taps into the process by which ongoing goal-directed behaviour can be influenced by encountering reward-paired cues and thus may reflect how cue-induced craving translates into active drug-seeking (Tiffany and Drobes 1990; Gawin 1991; O'Brien et al. 1998; Tomie et al. 2008). Evidence also suggests that the cues associated with drug-taking become CRfs and represent autonomous subgoals in their own right that are valued independently from the drug themselves (Williams 1994). This powerful observation helps explain why drug substitution therapy can combat the physiological symptoms associated with drug withdrawal but does not necessarily reduce craving and the desire to use; the addict still yearns for the sensory experience triggered by the drug-paired cues (Rose and Levin 1991; Naqvi and Bechara 2005, 2006). The degree to which individuals vary in their willingness to work for CRfs may therefore have a direct relationship to relapse vulnerability, particularly at timepoints distal to cessation of use, long after physiological withdrawal has passed. Interestingly, responding for CRfs is higher in rats during adolescence, a developmental period associated with higher vulnerability to addiction (Burton et al. 2011).

While PIT, CRf and sign-tracking tasks all provide valuable information into the ways in which cues modulate behaviour, they are somewhat removed from the specific type of decision-making that is recruited in the context of gambling and even relapse to addiction. Furthermore, although ST, PIT and CRf may look superficially quite similar, they depend on somewhat distinct neural and neurochemical systems that nevertheless overlap with those involved in addiction and affective decision-making within limbic corticostriatal loops (Cardinal et al. 2002). Given that very similar-looking cue-dependent behaviours can depend on dissociable neurobiological substrates, the question then remains as to whether the influence of cues in more complex cognitive processes, such as the kinds of cost/benefit decision-making involved in gambling behaviour, is subject to similar or distinct regulatory mechanisms.

3.6 *The Addition of Cues to Decision-Making Tasks Fundamentally Alters Neurobiological Regulation of Choice*

Although there are few reports of animal models in which the presence or absence of cues on decision-making has been explicitly studied, one exception is the delay-discounting model of impulsive choice. In this paradigm, animals choose between smaller-sooner versus larger-later rewards, thereby modelling the degree to which delay to gratification affects the subjective appraisal of reward value (see Mazur 1997 for review). If a cue light is illuminated during the delay, rats become less impulsive (Cardinal et al. 2000; Zeeb et al. 2010). Interestingly, whereas lesions or inactivations of the orbitofrontal cortex (OFC) decrease impulsive choice in the absence of the cue, the opposite pattern of results is observed if the delay is cued, and this increase in impulsive choice is most prominent in animals showing lower levels of impulsivity at baseline, i.e. those that were arguably using the cue to mitigate the negative impact of the delay (Zeeb et al. 2010). The role of the OFC in decision-making therefore appears particularly sensitive to the presence of cues, but whether this can be attributed to CRf mechanisms is currently unknown. Given that the cue is presented only after a response, it seems unlikely that ST or PIT would be acutely involved on a trial-by-trial basis. However, acquisition of complex operant tasks likely involves the formation of numerous associations, not all of which are immediately obvious to, or intended by, the experimenter. ST has been associated with impulsive choice even on an uncued delay-discounting paradigms (Flagel et al. 2010), implying there may be some neurobiological or phenomenological overlap between these processes.

With respect to addiction, one important consideration is the way that drugs of abuse boost the power that reward-paired cues have on behaviour due to hyper-stimulation of the dopamine (DA) system. Although not the only neurochemical system implicated, DA's influence is certainly the most well-established, and the nucleus accumbens (NAC) the neural target of most intensive study. Natural rewards simulate the firing of DA neurons in the mesolimbic pathway, but if those rewards are reliably predicted by a CS, this firing switches to presentation of the cue (Schultz et al. 1997; Schultz 1998; Clark et al. 2013). Increasing DA release actively recruits the NAC into the process of responding for CRf- under baseline conditions, lesions to accumbal regions have no effect on this behaviour (Taylor and Robbins 1984, 1986; Cador et al. 1991; Parkinson et al. 1999; Cardinal et al. 2002). Similarly, PIT can be enhanced by intra-NAC amphetamine and abolished by DA antagonists (Dickinson et al. 2000), and ST is likewise sensitive to DAergic manipulations of the NAC (Wyvell and Berridge 2000; Di Ciano et al. 2001; Dalley et al. 2002, 2005). Clearly changing DA signalling enhances the role of the NAC in cue-sensitive behaviours, but the addition of cues can likewise make behaviour DA-dependent. Administration of DA antagonists directly into the OFC only decreased impulsive choice in the cued version of the delay-discounting task,

theoretically by reducing the ability of the cue to promote choice of the larger delayed reward (Zeeb et al. 2010).

Although systemic administration of DA receptor-type 2/3 $D_{2/3}$ antagonist moderately improved choice on the rGT, neither chronic nor acute administration of $D_{2/3}$ agonists impacted behaviour (Zeeb et al. 2009; Tremblay et al. 2013). The findings are in stark contrast to the ability of such drug regimens to enhance risky choice on a simpler test of preference for uncertainty, in which both cues and striatal $D_{2/3}$ receptors play a prominent role (Cocker et al. 2012; Tremblay et al. 2013). Furthermore, administration of the selective DA reuptake inhibitor GBR 12909 did not affect decision-making, although co-administration of this agent with the selective noradrenaline reuptake blocker did mimic the deleterious effects of amphetamine (Baarendse et al. 2012). In addition, while both D1 and D2-family antagonists can attenuate impulsive responses caused by amphetamine, neither of these compounds could attenuate amphetamine-induced impairments in choice (Zeeb et al. 2013). In sum, choice behaviour on the rGT does not seem to be predominantly driven by the DA system. While this may not alter the utility of the task in modelling decision-making under uncertainty, it may impact the ability of the task to accurately approximate certain aspects of pathological engagement in risky decision-making. The evidence reviewed above indicates that the addition of reward-paired cues may improve not only the face validity of the rGT, but also the construct and predictive validity of this paradigm.

In order to explore this hypothesis, we therefore disproportionately cued wins on the rGT's disadvantageous options to see whether these cues can shift animals' decision-making preferences (Barrus and Winstanley 2014, 2015). The pairing of salient cues to disadvantageously risky options is similar to human gambling paradigms in which large, often risky wins are more saliently cued than small wins or losses. The structure of the cued rGT was identical to that of the traditional rGT, save the introduction of salient cues to winning trials. On the cued rGT, a loss on any option was identical to a loss on that same option on the traditional rGT. However, while a win on the rGT was marked by the allocation of sucrose pellets and the solid illumination of the tray light, a win on the cued rGT was additionally marked by a combination of tones and flashing light. Although all wins, large or small, were accompanied by an audiovisual cue of equal length and intensity (i.e. brightness and loudness), the cues associated with the larger rewards were more complex and variable. Just as in a human gambling paradigm, the salience of the win-associated cues therefore increased with the size of the win.

Results to date indicate that animals performing the cued rGT adopt a riskier, more disadvantageous choice strategy than those on the uncued task (Barrus and Winstanley 2014). These results demonstrate that salient, audiovisual win-paired cues are sufficient to enhance choice of riskier, more disadvantageous options, thereby modelling the negative impact such cues may have on human choice. Furthermore, the presence of such cues alters the way in which certain dopaminergic ligands, namely those acting at subtypes of the D_2 receptor family, impact decision-making. While D_2- and D_4-selective agents were without effect on either version, choice on the cued task appears uniquely sensitive to modulation by DA

D_3 receptor ligands; D_3 agonism increased choice of the high-risk option associated with maximal uncertainty with respect to the delivery of reward or punishment, whereas D_3 antagonism had the opposite effect (Barrus and Winstanley 2015submitted). These compounds did not affect choice in the uncued paradigm (Di Ciano et al. 2015; Barrus and Winstanley 2015 submitted). Numerous studies specifically implicate D3 receptors in mediating the maladaptive influence of cues in substance use disorder, and recent data posit a critical role for this receptor subtype in GD (Le Foll et al. 2014; Lobo et al. 2015). The cued rGT may therefore provide a novel and relatively unique method to empirically determine the degree to which cue-sensitivity can promote poor choice in a cost/benefit model in a manner central to the addiction process.

3.7 Concluding Remarks

Associative learning is one of the fundamental building blocks of advanced cognitive processes. The degree to which associations are formed between cues and outcomes clearly shapes behaviour in both relatively simple ways, as in basic classical conditioning procedures, but also in more complex paradigms. The ability of drug-paired cues to influence drug-seeking and ongoing goal-directed behaviour lies at the heart of current theories of chemical dependency and has been investigated in tightly controlled animal experiments. The study of gambling in humans indicates that the numerous, salient, audiovisual cues used in commercial gambling scenarios can invigorate behaviour, but it is unclear whether these cues have as fundamental role to play in GD as they are theorized to have in drug addiction. Although much less is known about the importance of cues in processes relevant to the development of GD, recent data indicate that the presence of win-paired cues can bias animals towards risky choices and alter dopaminergic regulation of decision-making behaviour. Whether this cue-induced risky choice behaviour is driven by the same kinds of cue-driven behaviours as implicated in addiction (ST, PIT, CRf) remains to be experimentally determined. Understanding the similarities and differences in the motivational influence exerted by cues in chemical and behavioural addictions could further elucidate the degree to which these conditions can be considered homogeneous and therefore responsive to similar pharmacological and behavioural treatment interventions.

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