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A roadmap for transformative translational research on gambling disorder in the UK

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ABSTRACT

The UK has one of the highest rates of recreational gambling in the world. Some vulnerable individuals progressively lose control over gambling and develop at-risk gambling or gambling disorder (GD), characterised by the compulsive pursuit of gambling. GD destroys lives and incurs massive costs to societies, yet only a few treatments are available. Failure to develop a wider range of interventions is in part due to a lack of funding that has slowed progress in the translational research necessary to understand the individual vulnerability to switch from controlled to compulsive gambling. Current preclinical models of GD do not operationalise the key clinical features of the human condition. The so-called "gambling tasks" for non-human mammals almost exclusively assess probabilistic decision-making, which is not real-world gambling. While they have provided insights into the psychological and neural mechanisms involved in the processing of gains and losses, these tasks have failed to capture those underlying real-world gambling and its compulsive manifestation in humans. Here, we highlight the strengths and weaknesses of current gambling-like behaviour tasks and suggest how their translational validity may be improved. We then propose a theoretical framework, the incentive habit theory of GD, which may prove useful for the operationalisation of the biobehavioural mechanisms of GD in preclinical models. We conclude with a list of recommendations for the development of next-generation preclinical models of GD and discuss how modern techniques in animal behavioural experimentation can be deployed in the context of GD preclinical research to bolster the translational pipeline.

1. Introduction

1.1. Epidemiology, prevalence, cost to society, and state of therapy

Recreational gambling is common in the United Kingdom, with over half of the adult population thought to have participated in some form of gambling activity in the preceding year [e.g., electronic gambling machines (EGMs), online gambling, sports betting, lotteries, etc.] (HSE, 2023). The widespread accessibility of gambling has substantial negative implications for population health, since up to ~2 % of the population is at risk of developing full gambling disorder (GD) and another ~10 % of developing "at-risk gambling" (i.e., meeting some DSM-5 diagnostic criteria for GD). These statistics translate into a total economic cost of gambling-related harms that approaches £ 2 billion per year based on initial estimates, though actual costs are likely to be much higher (OHID, 2023). Compounding the problem, individuals diagnosed with GD, as well as those who exhibit at-risk gambling, are at heightened risk of psychiatric comorbidities, such as (but not limited to) alcohol or substance use disorder (AUD and SUD, respectively), anxiety disorders, depressive disorders, attention deficit/hyperactivity disorder (ADHD), and obsessive-compulsive related disorders (Lorains et al., 2011; Chamberlain et al., 2015; Quigley et al., 2015; Grant and Chamberlain, 2020).

Several psychotherapeutic treatments (e.g., cognitive behavioural therapy and exposure therapy) have been suggested to yield clinically relevant effects for the treatment of GD (Ribeiro et al., 2021). However,

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the effect of these treatments has often been compared to a control condition of a 'waiting list,' which can artificially inflate the apparent effect sizes of such active interventions (Laws et al., 2022). There is no consensus as to which approach is most efficacious, perhaps partly due to a lack of granular understanding of the behavioural mechanisms underlying GD (Potenza et al., 2019).

Similarly, while a comprehensive systematic review of clinical trials dating back to 1980 originally suggested that opioid receptor antagonists (e.g., nalmefene and naltrexone, which is actually a weak partial agonist), selective serotonin reuptake inhibitors (SSRIs), and N-acetylcysteine (NAC) (which restores glutamatergic homeostasis) had therapeutic potential for the treatment of GD (Kraus et al., 2020); a recent systematic review and network meta-analysis of randomized controlled trials (RCTs) confirmed that only the opioid antagonists nalmefene and naltrexone were superior to placebo (Ioannidis et al., 2023). However, these two medications were associated with relatively high levels of dropout due to side effects, highlighting the need for alternative options. Thus, the current pharmacotherapeutic arsenal for GD is limited, likely because the current drugs do not necessarily target enough the core neurobiological processes underlying GD and also because their side effects lead to a relatively high attrition rate (Ioannidis et al., 2023; Chamberlain et al., 2024).

It is clear that a deeper mechanistic understanding of the psychological and neurobiological basis of the development of GD and at-risk gambling is necessary for the development of new and more effective targeted preventive and therapeutic strategies. Understanding these mechanisms may also help identify the features of modern gambling modalities [e.g., electronic gambling machines (EGMs) and virtual online gambling] that make them particularly addictive (Delfabbro et al., 2020). Reaching this new frontier in GD research depends on the development of an ambitious, innovative, and integrated national programme of translational research. The statutory levy on gambling operators recently imposed by the UK government that is expected to yield £100 million for gambling harms research, treatment, and prevention (UK Department for Culture, 2024) is one of the first of its kind worldwide, and represents a unique opportunity to fund ambitious and disruptive programmes of preclinical gambling research at a national level. Here, we propose a roadmap for transformative translational research on GD that considers the psychological nature of GD, outlines the limitations of present preclinical models of GD, and proposes a new biobehavioural theoretical framework of compulsive behaviours, namely the incentive habit theory, to help design novel preclinical models of GD. This roadmap we hope, may help shape innovative translational GD research in the UK and beyond.

1.2. Lessons from AUD and SUD in the utility of preclinical models

The characterisation of the biobehavioural antecedents and consequences of GD and at-risk gambling requires prospective longitudinal animal studies that can identify the targetable systems, circuits, cellular, and genetic profiles of GD. These studies must be grounded in preclinical models of GD that have strong construct and predictive validity, as well as heuristic value with regard to the human condition. This approach has already bore fruits in our understanding of the etiopathogenic and pathophysiological mechanisms of AUD and SUD, leading to a series of discoveries that have systematically been validated in humans that include the following:

1. **Behavioural vulnerability factors.** The identification of sensation seeking and impulsivity as factors that predict the tendency to engage in drug use and the vulnerability to switch from controlled to compulsive use, respectively, (Ersche et al., 2010, 2013) was first made in rats (Belin et al., 2008).
2. **Neurobiological substrates and mechanisms.** As later discussed, drug seeking in humans, which is under the control of conditioned reinforcers such as money (Koob, 2021), becomes habitual before it turns into a compulsion in vulnerable individuals, [e.g., it persists in the face of adverse consequences (Everitt and Robbins, 2013, 2016; Luscher et al., 2020; Robbins et al., 2024)]. The functional engagement of the dorsolateral striatum dopamine-dependent mechanisms underlying the development of such habits (Volkow et al., 2006; Vollstadt-Klein et al., 2010; Cox et al., 2017) was discovered to precede the development of cocaine use disorder (Cox et al., 2017) and to predict relapse in those with a diagnosed SUD (Zilverstand et al., 2018) long after its characterisation in non-human primates (Porrino et al., 2004) and the causal characterisation of its significance in rodents trained to seek drugs under the control of the conditioned reinforcing properties of drug-paired conditioned stimuli (Vanderschuren et al., 2005). Similarly, preclinical research has substantially contributed to the understanding of the neural mechanisms of different stages of the addiction cycle (Koob and Volkow, 2016; Volkow et al., 2016), including the role the amygdala-striatal system, and that of GABAergic mechanisms and an associated polymorphism in the amygdala, in AUD and SUD (Ito et al., 2002; Volkow et al., 2006; Belin and Everitt, 2008; Vollstadt-Klein et al., 2010; Belin et al., 2013; Murray et al., 2015; Cox et al., 2017; Augier et al., 2018; Zilverstand et al., 2018; Giuliano et al., 2019; Puaud et al., 2021; Hynes et al., 2024a; Robbins et al., 2024).

A new generation of preclinical animal models, rooted in the psychological and behavioural determinants of the diagnostic criteria for GD, can be similarly used to causally identify the behavioural vulnerability factors and neurobiological substrates of GD. Such models could furthermore identify the behavioural, neural, and neurochemical signature of putative pro-addictive features of modern gambling modalities (e.g., high arousal maintained by unpredictability and salient audiovisual stimuli, losses disguised as wins, probabilistic decision making, etc.) (Clark, 2010; Baudinet and Blaszczynski, 2013; Barton et al., 2017).

Combined with contemporary neuroscience techniques such as fibre photometry (Cui et al., 2014), chemo- and opto-genetics (Boyden et al., 2005; Lee et al., 2014), animal models will also uniquely enable the measurement and causal manipulation of the activity of identified brain circuits in adaptive and maladaptive gambling behaviour with a level of precision that is impossible in human beings. Such techniques, have successfully offered a circuit-level mechanistic understanding of the therapeutic effects of neurostimulation techniques, such as repeated transcranial magnetic stimulation, for the treatment of cocaine use disorder (Chen et al., 2013; Terraneo et al., 2016; Madeo et al., 2020; Pettorruso et al., 2020). Deployed in combination with valid animal models of GD, these neurotechnologies will contribute to translational psychiatric research with the potential to transform our basic understanding and therapeutic approach to GD and GD-adjacent conditions.

1.3. Pharmacotherapy in preclinical models of gambling-like behaviour – lost in back translation?

Many behavioural procedures have been developed in non-human animals that assess individual differences in decision-making, risk-taking, sensitivity to losses, or the arousing properties of different types of reward-related cues (Simon et al., 2011; Rogers et al., 2013; Floresco et al., 2018; Cocker et al., 2019; Langdon et al., 2019; Winstanley and Hynes, 2021). These procedures have yielded invaluable insights into the psychological, behavioural and neurobiological mechanisms of decision-making and risk-taking, such as the demonstration of an interaction between psychotropic drug use (e.g., cocaine, cannabinoids, and therapeutic dopamine agonists) and risk-taking (Cocker et al., 2020; Brodie et al., 2023; Mortazavi et al., 2023; Hynes et al., 2024b) or the identification of the role of the mesolimbic dopamine system, basolateral amygdala, and frontal cortex in decision making (Ghods-Sharifi et al., 2009; Hynes et al., 2020, 2021, 2024b; van Holstein and Floresco, 2020); and that of interoception, stress, and impulsivity in decisional

strategies (Barrus et al., 2015; Daniel et al., 2017; Gabriel et al., 2019; Bryce et al., 2020). However, a preclinical model of GD that captures the hallmark features of the disorder in humans, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013), for instance, has not yet been developed. This may explain why drugs that show some promise in the treatment of GD have no effect on what is commonly called gambling like behaviour (GLB) in rats. For instance, using the rat gambling task (rGT), considered by many a gold standard assay of GLB in the rat, naltrexone was found to have no or non-clinically relevant effect(s) on behaviour (Di Ciano and Le Foll, 2016; Tjernstrom and Roman, 2022). The SSRI citalopram similarly has no effect on performance in the rGT (Baarendse et al., 2013), which was instead *exacerbated* by direct agonism of the 5HT1A receptor (Zeeb et al., 2009).

In conjunction with an initial course of psychotherapy, NAC resulted in better long-term outcomes than therapy plus placebo in patients with GD and nicotine dependence (Grant et al., 2014), however the effect of this drug on GLB in non-human animals has not been explored. While other drugs that target the glutamatergic system have been shown to not influence GLB (Tremblay and Winstanley, 2016), NAC has been shown to decrease several SUD-like behaviours in rodents (Zhou and Kalivas, 2008; Murray et al., 2012; Ducret et al., 2016; Hodebourg et al., 2019). Together with the evidence that NAC has therapeutic efficacy in controlled human trials for other compulsive disorders such as hair-pulling disorder and skin-picking disorder (Grant et al., 2009, 2016; Bloch et al., 2013), these reports warrant further investigations into the potential therapeutic potential of NAC in the context of GD.

Conversely, the therapeutic potential in GD of drugs that have been shown to influence GLB has not been thoroughly investigated. While pharmacological modulation of the dopamine system profoundly influences GLB (Simon et al., 2011; Winstanley et al., 2011; Schumacher, 2020; Winstanley and Hynes, 2021; Mortazavi et al., 2023; Hynes et al., 2024b; Wheeler et al., 2024), the clinical outcome of the single available study on the effect of antipsychotic medication on GD and problem gambling was underwhelming (Ioannidis et al., 2023). However, open-label treatment with the COMT inhibitor tolcapone, the effect of which on GLB in rodents has not yet been reported, was associated with reductions in symptom severity in patients with GD (Grant et al., 2013; Schacht et al., 2022). Interestingly, the effect of tolcapone on GD symptoms in this trial was predicated on a specific polymorphism of the COMT gene, exactly as for the efficacy of this drug in patients with AUD.

Such a lack of pharmacological isomorphism serves as a litmus test that may indicate poor construct and predictive validity of animal models of GD. The lack of translational validity of current animal models of GD may prevent the identification of novel druggable targets for the treatment of GD while highlighting that the psychological, behavioural, and neurobiological mechanisms measured and manipulated in the current suite of models of GLB, while being highly relevant to our understanding of decision making and risk-taking, may not be that informative with regards to that of human GD. This may require stepping back a little and, through the lens of learning theory, critically assessing what the next-generation animal model of GLB should have that the present ones lack. This will inform the design of a truly translational battery of animal models of GD.

2. Behavioural characteristics of gambling disorder – focus on DSM-5

The first step toward developing a translationally effective battery of animal models of GD is to define precisely the behavioural and psychological determinants of GD, which are encapsulated in the diagnostic criteria of the disorder. The DSM-5 outlines nine inclusionary criteria for GD (American Psychiatric Association, 2013), each of which describes a unique clinically measurable behavioural characteristic that aids in the diagnosis and assessment of the severity of GD. The severity of GD scales from mild to severe as the number of these criteria met by the patient increases from 4 (threshold for GD diagnosis) to nine. Those meeting three or fewer of the criteria are instead considered to be experiencing 'problem gambling' (PG), also known as 'at-risk' gambling. In this section, we describe each of the diagnostic criteria for GD, the ways in which they are measured, and discuss how they have been or could be operationalized in animal models of GD.

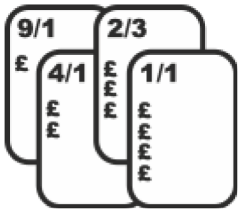
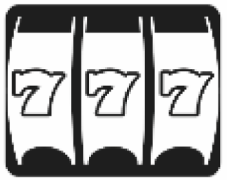
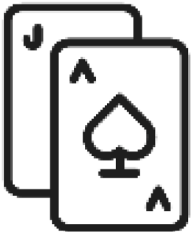
2.1. Compulsion

Gambling can exact an immense financial toll on people, quite often completely bankrupting them. The losses accrued from gambling are not only of financial nature, as gambling-associated behaviours (e.g., narrowing of interest, stealing from and lying to loved ones) can destroy relationships and be detrimental to the mental wellbeing of individuals who gamble and to that of their friends and family. The persistence of gambling in the face of such severe negative consequences, captured in the DSM-5 diagnostic criterion described as having "jeopardized or lost a significant relationship, job, or educational or career opportunity because of gambling,"is the behavioural manifestation of the compulsive nature of GD.

Compulsion has been successfully operationalised in animals models of OCD as the persistence of excessive coping responses despite adverse consequences to homeostasis (Belin-Rauscent et al., 2016; Moreno-Montoya et al., 2022) or physical integrity (Lamothe et al., 2023). In animal models of addiction, compulsion has first been operationalised as the persistence of an ingestive consummatory response despite adulteration of the outcome (often by addition of the bitter tastant quinine), as in compulsive alcohol drinking (Wolffgramm and Heyne, 1995; Hopf et al., 2010; Marti-Prats et al., 2021). For intravenously self-administered drugs, compulsive consumption is operationalised as the persistence of drug self-administration under fixed ratio schedules of reinforcement in the face of contingent footshocks, as in the 3crit multidimensional model of cocaine addiction (Deroche-Gamonet et al., 2004; Belin et al., 2008).

It is important to note the imposition of an electric footshock in a procedure does not always assess whether the instrumental response is compulsive. Depending on the contingency, the electric shock, which is otherwise a clear punisher, can acquire appetitive properties through counter-conditioning (Dickinson, 1975), and, unfortunately, many so-called studies claiming to assess compulsion suffer from this flaw. Additionally, the introduction of electric shocks in opiate self-administration is problematic because of the analgesic properties of these drugs. In this case, it is much better to punish drug seeking (Fouyssac et al., 2025; Jones et al., 2024). Here it is essential to clearly define seeking responses and how to operationalise them. A preparatory instrumental seeking response is a learnt and well-rounded response expressed over a period of time in the absence of the reinforcer, with the aim of eventually procuring and consuming the said reinforcer. In the case of drug foraging or gathering money for gambling, the preparatory seeking behaviour can persist for long periods, even when reinforcement is scarce. Procedures that spatially or temporally dissociate preparatory seeking from taking or consummatory responses, such as the seeking-taking-drinking task for alcohol (Giuliano et al., 2019) and fixed interval or second-order schedules of reinforcement with long intervals (the longer the interval, the longer the seeking period) (Goldberg, 1973; Kelleher and Goldberg, 1977; Spealman and Goldberg, 1978; Everitt et al., 2018), enable the assessment of ecologically valid seeking behaviour in a parametrically controlled manner in humans, non human primates and rodents (Everitt and Robbins, 2000; Lamb et al., 1991). Unfortunately, some have argued that seeking responses can be measured as long as they are assessed when the outcome is not present, as is the case under extinction, or in so-called reinstatement of seeking tasks. Seeking responses, by definition, do not drop over time as they do under extinction, because the organism has learnt that persisting in foraging will bring the outcome about. The organism does not learn that the response now leads to no outcome, which is the new

Box 1
Current animal models of gambling-like behaviour.

	Rat Gambling Task	Risky Decision Making Task	Rat Slot Machine Task	Rat Blackjack Task	Loss Chasing Task	Rodent Balloon Analogue Risk Task
						
Description	Animals choose between four options, each with a unique magnitude of reward and probability of winning or losing. The larger the potential reward, the more likely a loss is to occur.	Animals have the option of responding for a small reward with 100 % certainty of winning or a large reward with a probability of receiving an electric shock instead. The likelihood of electric shock increase over trials.	Animals initiate the random illumination of any combination of an array of three lights. The illumination of three adjacent lights signals a winning opportunity. To win, animals must respond during winning opportunities and thereby learn to distinguish a winning combination from "near misses" (i.e., two adjacent illuminated lights).	Animals have the option of selecting a small reward with 100 % certainty of winning or a large reward with a probability of losing. The probability of losing changes and is explicitly signalled by discriminative auditory stimuli.	Animals respond for the probabilistic delivery of a reward (7/3 - win/loss). In the event of a loss, animals are given the option to take the loss or chase the loss by making a different response which doubles the magnitude of the potential reward but also increases the probability of losing (1/1 - win/loss).	Animals accumulate potential rewards by making one response and deliver the accumulated rewards by making a different response. The probability that all accumulated rewards will be lost increases as the reward cache builds.
Seminal (Jentsch et al., 2010)	Publication	(Zeeb et al., 2009)	(Simon et al., 2009)	(Cocker et al., 2016)	(Floresco et al., 2018)	(Rogers et al., 2013)

context-dependent association that instead underlies extinction, alongside a weakening of the original response-outcome association. If it was the case, the organism would quickly give up and never obtain the outcome. If the mechanisms that underly responding under extinction are those involved in the seeking of alcohol, other drugs, or gambling in real life, our present discourse on the matter would be moot, as AUD, SUD, and GD would not exist. In reality, individuals must engage in long sequences of seeking behaviour, after which they obtain and consume their sought-after drug or gambling experience, a psychological process of which the idiosyncratic extinction-reinstatement procedure does not capture. In CS-induced reinstatement procedures, what is reinstated is an extinguished taking response, not a seeking response. The animal faces for the first time in their life a situation in which a response that it knows no longer results in the outcome now produces and outcome-associated Pavlovian cue. Thus, the animal learns to respond for the conditioned reinforcing properties of the CS while simultaneously learning to extinguish this association since the US is never presented. In extinction-reinstatement procedures, the episode of reinstatement of the extinguished response by the CS is therefore only transient, lasting at best 10 minutes.

In contrast, adaptations of chained schedules or second-order schedules of reinforcement with the introduction of an electric shock contingent upon the seeking response successfully capture the persistent nature of compulsive seeking behaviour (Fouyssac et al., 2025; Giuliano et al., 2018; Jones et al., 2024; Pelloux et al., 2007; Vanderschuren and Everitt, 2004).

In the context of GD, at least one procedure, the risky decision-making task (RDT) (Box 1) has employed such design elements to probe the compulsive nature of gambling performance (Simon et al., 2009).

2.1.1. Escalating bets

Over the course of the development of GD, many report the need to increase the amount of money wagered in order to gain the same level of satisfaction from gambling, a phenomenon that is akin to tolerance in substance use disorder (Blaszczynski et al., 2008). This criterion of GD is described in the DSM-5 as needing "to gamble with increasing amounts of money in order to achieve the desired excitement." Tools like the National Opinion Research Centre DSM Screen for Gambling Problems (NODS) pose questions such as "Have there ever been periods when you needed to gamble with increasing amounts of money?" to evaluate this criterion (Gerstein et al., 1999).

Several studies using The Rat Gambling Task (rGT) (Box 1) have captured behaviours that may share common psychological mechanisms with this facet of GD, showing that over the course of the development of GLB, the frequency with which rats make risky "bets" increases (Hynes et al., 2021, 2024b; Mortazavi et al., 2023).

2.1.2. Withdrawal symptoms

A voluntary or forced reduction in or complete abstinence from gambling precipitates a negative affective state characterized by irritability, restlessness, or anxiety in may people with GD (Blaszczynski et al., 2008). Clinicians use techniques ranging from semi-structured interviews (Turner et al., 2008) to physiological measures [i.e., heart rate monitoring (Griffiths, 1993b)] to measure gambling withdrawal.

Though there have been no reports of withdrawal induced by cessation of GLB in animals, behavioural [e.g., anxiety as assessed on the elevated plus maze (Knapp et al., 2004)] and physiological markers [e.g., cortisol levels (Zorrilla et al., 2001)] following abstinence from protracted GLB could be applied similarly to how they are in preclinical SUD research.

2.1.3. Relapse

Even though people with GD may manage to completely stop or reduce the frequency with which they gamble, a large proportion of them are unable to do so for an extended period of time and often resume gambling, despite their explicit goal to remain abstinent (Hodgins and el-Guebaly, 2004; Ledgerwood and Petry, 2006). The NODS features the item "Have you ever tried but not succeeded in stopping, cutting down, or controlling your gambling?" to assess gambling relapse.

Relapse-like behaviour has not been investigated in animal models of GD, though traditional extinction-reinstatement models would be as insufficient here as they are in preclinical models of relapse in SUD, as previously discussed. In these models, abstinence is achieved through operant extinction (Bossert et al., 2013); this assumes that the reinforcing effect of the drug is the primary motivational factor in SUD. Though evaluating the validity of this assumption in SUD is beyond the scope of this review, withholding the primary reinforcer of gambling (i.e., money) clearly does not lead to abstinence from gambling, as losses occur far more frequently than wins in the real world. In the real world, voluntary abstinence from gambling usually occurs, as it does in the case of AUD or SUD, when the negative consequences become too severe. Involuntary abstinence may occur when the individual runs out of money to gamble with. The former could be operationalised in animals by imposing a progressively increasing aversive consequence (i.e., an electric shock), as with the conflict model of drug self-administration (Zumbusch et al., 2023). The latter may be modelled by observing invigorated gambling seeking behaviour after withholding the opportunity to gamble for an extended period of time (Fouyssac et al., 2022).

2.1.4. Stress-related gambling

For some, gambling serves, at least originally, as a coping strategy (i.e., as a means to reduce negative affective states arising from stressful life events). Many people with GD indeed report a decrease in the symptoms of anxiety and depression while engaging in gambling (Donnelly, 2009), thereby revealing that negative reinforcement can be a primary mechanism by which gambling can be initiated and perpetuated. The DSM-5 criterion that captures this element of GD is "gambles as a way of escaping from problems or of relieving a dysphoric mood (e.g., feelings of helplessness, guilt, anxiety, depression)." If the source of this stress is gambling withdrawal, this phenomenon may further negatively reinforce gambling behaviour and promote relapse during times of abstinence. Through Pavlovian mechanisms, stress can also act as an interoceptive conditioned stimulus that triggers relapse (Coman et al., 1997). Stress-related gambling is assessed in human clinical populations via self-reports and questionnaires, such as The Gambling Pathways Questionnaire (Nower and Blaszczynski, 2017).

In animal models of GD, prior exposure to inescapable physical stress [The Rat Gambling Task (RGT) (Nobrega et al., 2016)] (Box 1) or pharmacological stressors [Blackjack Task (BJT) (Bryce et al., 2020)] (Box 1) have been shown to potentiate GLB. It is still unclear from these studies whether, if either, negative reinforcement-based stress coping or Pavlovian stress-induced GLB is the underlying mechanism.

2.1.5. Loss-chasing

After incurring a financial loss from gambling, some individuals will continue to gamble in order to win back that which they have lost. This phenomenon of "loss-chasing" is captured in the DSM-5 GD criterion of "after losing money gambling, often returns another day to get even." The NODS and GPQ both feature items that assess loss-chasing, yet these tools only assess between-session loss-chasing (i.e., returning another day or time). Critically, there are behaviourally heterogeneous expressions of loss-chasing that are not captured in these self-report tools (Banerjee et al., 2023).

Within-session intensification of gambling behaviour following a loss also occurs in human populations and is the subtype of loss-chasing that has hitherto been explored in animal models. Within-session loss-chasing is the main behaviour of interest in the rodent loss-chasing task (LCT) (Box 1) (Rogers et al., 2013). Loss-chasing has been indirectly assessed in the RGT, BJT, and RDT via win-stay/loose-shift analyses, where the trial-by-trial tendency to persist on high-risk/high-reward

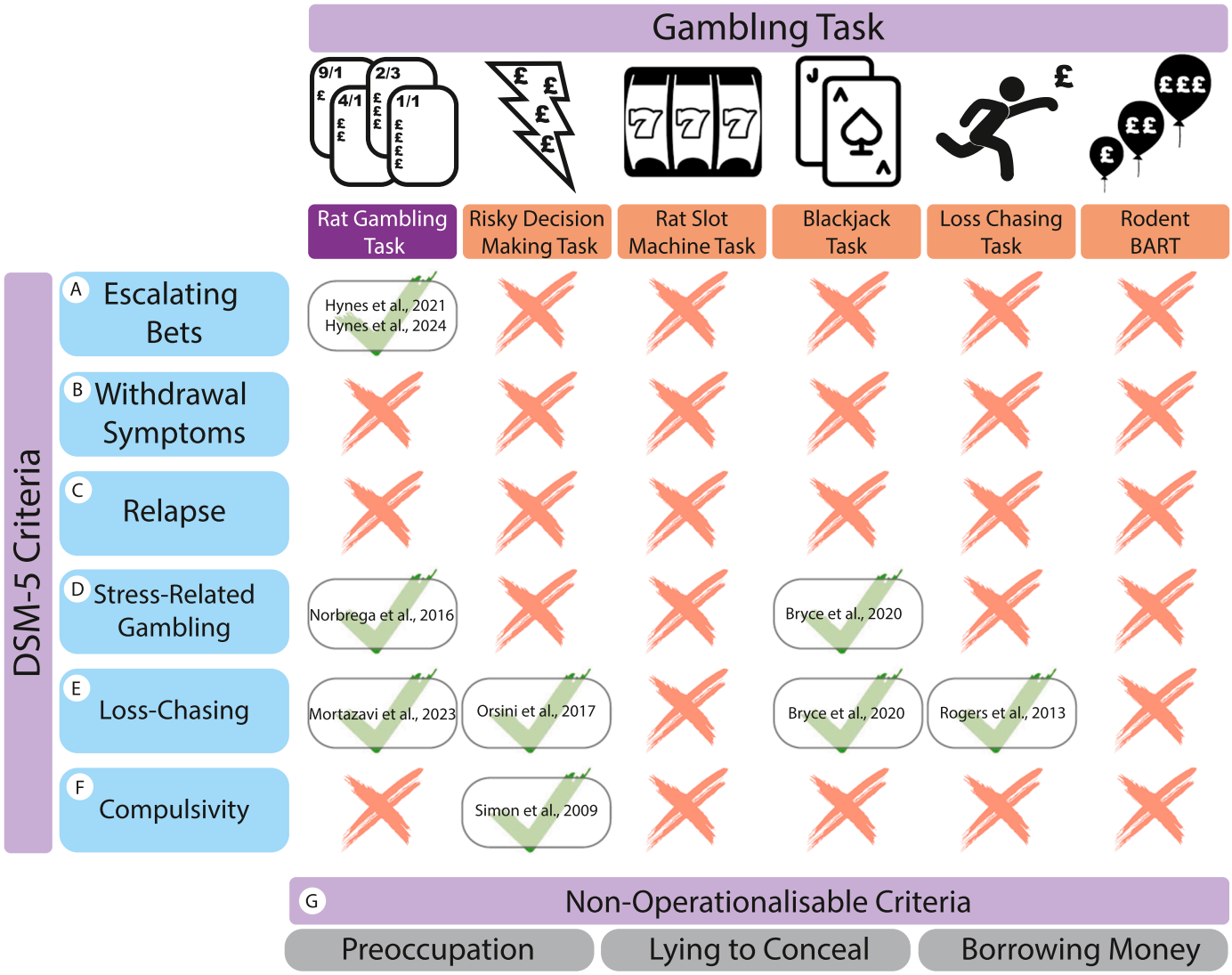


Fig. 1. Gambling-relevant behavioural mechanisms are poorly characterized in contemporary models of GD. In addition to lacking many of the structural elements of real-world gambling, each preclinical assay of GD captures at most three DSM-5 diagnostic criteria for GD. (A) The criterion of making increasingly large wagers over time is captured in two longitudinal rat gambling task studies, where a subset of made progressively risker choices over time (Hynes et al., 2021, 2024b). (B) No GD-relevant task in the rat models withdrawal, though physiological (e.g., cortisol levels, heart rate, hypodopaminergia, etc.) or behavioural (e.g., anxiety- and depressive-like behaviours) readouts could be collected during forced-abstinence from engaging in GLB. (C) No task of gambling like behaviour has modelled inability to abstain from gambling for long periods, yet this phenomenon could be examined by having to abstain from GLB either forcefully or voluntarily (e.g., by means of imposing negative consequences for gambling) and then observing whether a relapse-like "rebound" characteristic of a compulsion to engage in gambling behaviour occurs when rats are again given the opportunity to engage with the task. (D) Various physical and pharmacological stressors increase GLB in the rGTand BJT, mimicking the clinical observation that those with GD gamble more when they are feeling distressed (Nobrega et al., 2016; Bryce et al., 2020). (E) While the LCT explicitly operationalises the diagnostic behavioural phenomenon of loss-chasing (Rogers et al., 2013), win-stay/loose-shift analyses performed in the rGT (Mortazavi et al., 2023), RDT (Orsini et al., 2017), and BJT (Bryce et al., 2020) also provide insight into whether rats continue to select high-reward options after losing. (F) The compulsive nature of GD (i.e., continued gambling despite negative consequences) is approximated only in the RDT, where some animals exhibit GLB despite electric shock (i.e., acute positive punishment). Nevertheless, this approximation does not capture the severe and long-lasting negative punishment and sometimes complete financial and social bankruptcy endured by those with GD. In summary, the rGT encapsulates most of the DSM-5 diagnostic criteria for GD, but still falls short. However, several modifications to the rGT task structure could make it such that all criteria are covered. (G) The mental preoccupation with gambling, lying to conceal one's gambling behaviours, and borrowing money from others to support a gambling habit are criteria that would be difficult, if not impossible, to operationalize from observed animal behaviour, at least now.

options is assessed in both within-session (Orsini et al., 2017; Bryce et al., 2020; Chernoff et al., 2024) and between-session RGT (Mortazavi et al., 2023). However, a poor lose-shift score has also been associated with decreased sensitivity to negative feedback and impaired flexibility (Bari et al., 2010; Rayburn-Reeves et al., 2013) which may only partially, if at all, account for loss chasing.

Although we are optimistic that animal models of gambling can be evolved to model human gambling with such proximity that they may inform therapeutic development, the degree to which current animal models of GD reflect DSM-5 criterion for GD is, at present, lacking (summarized in Fig. 1); though as we have discussed here, it would be relatively straightforward to operationalise most of the criteria moving forward. There are, however, three DSM-5 criteria that seem impossible to model in rodents.

2.1.6. Preoccupation

Many people with GD or PG spend an inordinate amount of time thinking about gambling, such as reminiscing past gambling

experiences, contriving ways to acquire money for gambling, or planning their next opportunity to gamble. In the DSM-5 criteria for the diagnosis of GD, preoccupation with gambling is defined as "preoccupied with gambling (e.g., preoccupied with reliving past gambling experiences, handicapping or planning the next venture, or thinking of ways to get money with which to gamble)." We do not think it is possible yet to investigate, in non-verbal animals, mental states that can only be assessed through subjective reports in humans.

2.1.7. *Lying to conceal*

When gambling becomes a subject of personal shame or a behaviour that draws disapproval from others, people with GD or PG lie to conceal the extent of their gambling. The DSM-5 describes this behaviour as "lies to family members, therapist, or others to conceal the extent of involvement with gambling." It is unknown whether rodents feel shame or are concerned with how their conspecifics perceive them, so the behaviour of lying cannot, as of today, be assessed in rodents.

2.1.8. *Borrowing money*

In order to relieve their dire financial situation or to gain money to engage in further gambling, a proportion of those with GD or PD will borrow money; described in the DSM-5 as "relies on others to provide money to relieve a desperate financial situation caused by gambling." Because the practice of currency exchange does not exist in rodents, models of borrowing to gamble would be impossible to develop.

3. Contemporary animal models of gambling-like behaviour

3.1. *Critical introduction to contemporary animal models of "gambling"*

In the first laboratory behavioural task where animal behaviour was operationalized as "gambling," pigeons were given the choice of a guaranteed piece of food for pecking a button 30 times or a 50 % chance of getting food from another button that needed only to be pecked 10 times (Kendall, 1987). In this task, some of the pigeons went for the risky choice, while others preferred the guarantee of food, suggesting even animals exhibited individual variability in the propensity to engage in so-called "gambling".

Of course, this task did not capture the essence of gambling, least in the behavioural domains most characteristic of GD, such as compulsion [i.e., the persistent engagement in a behaviour that is detrimental to the individual despite obvious negative consequences, such as bankruptcy (Robbins et al., 2024)]. Pigeons did not have anything to lose. They never risked going bankrupt or even losing precious calories, as they were still fed in between sessions. Instead, this task operationalised probabilistic decision making, or the individual tendency to maximise outcome under uncertainty, which has since become paradigmatic of most contemporary animal models of GLB.

The most influential and highly cited non-human gambling task is *The* Rat Gambling Task (rGT), two versions of which were developed around the same time (Rivalan et al., 2009; Zeeb et al., 2009). This task, which has become the gold standard, is loosely based on, and named after the influential decision-making task developed by Bechara and Damasio, the Iowa Gambling Task (IGT) (Bechara et al., 1994). In the IGT, participants are presented with four decks of cards, from which they can pick 100 cards, one at a time, with no prior instruction other than they should make a profit. Two of the decks yield a high immediate gain, and the other two decks yield a smaller gain. For each card drawn, there is a set probability (deck dependent) of having to pay a penalty as well, with the penalty being greater for the former two than the latter two decks. Thus, while the former two decks are initially appealing, in the long run, they result in a cumulative loss that outweighs the gains, and are therefore disadvantageous. In contrast, the other two decks are advantageous in the long run. Participants usually initially sample between the 4 decks of cards, with a bias towards those yielding greater immediate gains. Typical participants progressively move away from the disadvantageous decks, eventually preferring the less appealing but advantageous two decks. This reveals the ability to develop an internal model of the odds in the environment that enables maximisation of reward under uncertainty without necessarily having explicit knowledge of the model. Performance in the IGT, which depends on a network that involves the ventromedial, orbitofrontal and insular cortices (Lawrence et al., 2009), is impaired in individuals with GD (Cavedini et al., 2002), as well as those with AUD and SUD (Rogers and Robbins, 2003; Dom et al., 2005; Wilcox et al., 2016; Moorman, 2018; Campbell and Lawrence, 2021; Tabara et al., 2024). This shows that individuals with GD, AUD or SUD engage in sub-optimal decision-making, as is also suggested by their clinical symptomatology. However, this is by no means evidence that the IGT is a gambling task, and therefore neither is the rGT, one of the creators of which has been explicitly cautionary in this regard:

> "When considering how performance of tasks such as the IGT/rGT may be used to inform our understanding of behavioural addictions, there is a real danger of operationalizing risky decision-making as representative of GD (Winstanley and Clark, 2016)"

In the rGT, rats are allowed to sample between four options (four holes on a curved wall in which they can respond), which each having a unique probability of delivering a food reward of varying size or time-out punishment of varying length. The optimal strategy is to select those options which are likely to yield a small immediate food reward but are unlikely to yield a long time-out, thereby allowing rats to maximise the amount of food they earn within a specific time. At the population level, rats display a behaviour that is similar to that of humans: they first show an original preference for the two options that produce high immediate reward but progressively adjust their behaviour to prefer the more advantageous ones (Rivalan et al., 2009; Daniel et al., 2017). A minority of rats maintain a preference for the sub-optimal options, which despite yielding large food rewards, are more likely to result in long, unrewarded time-outs, yielding less food in the course of the session (Rivalan et al., 2009; Daniel et al., 2017). Evidently just like in humans, not all rats are equally able to maximise reward under uncertainty.

Substantial strides forward have been made to enhance the degree to which the rGT models the human behaviour of gambling, specifically insofar as the experimental conditions feature sensory elements that resemble the salient audiovisual stimuli of modern casino environments that are thought to enhance the addiction liability of gambling (Dowling et al., 2005; Dixon et al., 2014b). The Cued Rat Gambling Task (crGT) was designed to incorporate salient audio-visual stimuli reminiscent of those featured in modern casinos and electronic gambling modalities (Barrus and Winstanley, 2016). The addition of these stimuli was shown to worsen decision-making performance in GLB tasks. Investigations of the behavioural pharmacology of the crGT furthermore revealed that the neurobiological substrates of behavioural performance in the crGT more closely map onto those involved in gambling in humans (for review see Winstanley and Hynes, 2021). But still, the core behaviour in which these animals are engaging lacks too many of the features of real-world gambling to be deemed GD-like.

Gambling can take many forms, ranging from card games to EGMs to sports betting to lotteries and beyond, and it is challenging to consider that rat gambling tasks operationalise any of these modalities. The blackjack task (Floresco et al., 2018), on the other hand, intentionally aimed to operationalise in the rat a specific element of the popular casino card game from which the task takes its name. In casino blackjack, the odds of winning are influenced by the value of the initial hand dealt, which can, for instance, impact whether the player decides to "hit" or "stay." The initial hand thereby acts as a discriminative stimulus that influences the decision making of the player. A blackjack-like paradigm was designed for rats by giving them the option of responding on two levers – one that is certain to deliver a small food reward and another that *may* deliver a large food reward. The likelihood that the second

lever pays out is signalled by one of two distinct auditory cues, one indicating high probability and the other indicating low probability of winning. Much like a high dealer hand would cause a blackjack player to stay, the cue signalling poor odds in the blackjack task causes rats to choose the guaranteed option over the risky one. The creators of this task nonetheless took caution as not to overinterpret such behavioural phenomenology as representing a true animal model of casino blackjack and used the namesake only "colloquially" for their task (Floresco et al., 2018), as it resembles real blackjack only insofar as it features discriminative cue-guided decision making.

Another now highly cited and widely adopted rodent assay of decision-making coined the Risky Decision-Making Task (RDT) (Simon et al., 2009) was developed around the same time as the rGT. The RDT was designed to assess decision-making under probabilistic punishment. In this task, rats have the option of choosing between a lever that delivers a single food reward and one that delivers four food rewards, both 100 % of the time. Responding on the large, but not the small, reward-associated lever results in the probabilistic delivery of an aversive foot shock, a punishment the likelihood of which increases over time. This task does not obviously reflect any aspect of real-world gambling, but more closely resembles a punished variant of the delay discounting task (Myerson and Green, 1995; Winstanley, 2011); but here again, the creators of this task have never suggested that behavioural performance under these contingencies should be considered an operationalisation of gambling.

There exist other tasks that measure GLB in rodents that have gained less traction but may capture aspects of real-world gambling that are not by those previously discussed here. For instance, the rat slot machine task (rSMT) (Weatherly and Derenne, 2007; Peters et al., 2010; Winstanley et al., 2011) intends to capture in the rat the "near-miss effect," which refers to how the subjective experience of *almost* winning can encourage further gambling (Skinner, 1953), especially in those with GD (Clark et al., 2014). Take, for example, the situation where a line of slot machines delivers two identical symbols (e.g., cherry-cherry-bell) when three of a kind are needed to win (e.g., cherry-cherry-cherry). In such circumstances, individuals with GD or at-risk gambling may suffer from cognitive distortions resulting in the holding of an irrational belief that they are close to winning and, therefore, bet on a subsequent spin (Chase and Clark, 2010; Palmer et al., 2024). In attempting to operationalise this scenario, the rSMT presents rats with three adjacent illuminable holes, which, when they are all lit, set the occasion for a reinforced instrumental response (i.e., only when the three holes are lit does a lever press result in the delivery of a food reward). When any fewer than three are lit, responding now results in a time-out punishment. In a suggested demonstration of the near-miss effect, rats respond almost as frequently during two-light trials as they do for the three-light trials. Despite this apparent face validity, the cues are not response-produced, as they are in humans, and only act as discriminative stimuli. Perhaps even more importantly, the phenomenology of the rSMT may simply arise from stimulus generalization or relatively poorer stimulus discrimination in some individuals. Furthermore, the supposed near-misses of rSMT do not increase the frequency or vigour of gambling-like behaviour (Winstanley et al., 2011), as the formal definition of a gambling near-miss would require (Skinner, 1953; Pisklak et al., 2020). This task has relatively good face validity, in that it looks like the workings of a traditional slot machine, but face validity has long been suggested not to be relevant for the validation of preclinical models of psychiatric disorders (Geyer and Markou, 1995) for the reason that behavioural phenomenology cannot be assumed to be the same across species; in fact, it rarely is. The development of translational animal models should instead rely on construct and predictive validity; the latter lacking in current animal models of GD, as discussed below.

The rodent loss-chasing task (rLCT) (Rogers et al., 2013) is an ingenious paradigm with good construct validity, because it actually models the behavioural construct that it intends to – loss-chasing, another hallmark feature of GD that is characterized by the tendency to continue or even amplify gambling behaviour with the aim of recuperating previous losses (Lesieur, 1979; Dickerson et al., 1987). In this task, rats first respond in a single response hole, which results in the delivery of a food reward 70 % of the time. On the 30 % of trials where a loss is incurred, the rat is given the choice to endure a 4-second time-out punishment or to chase the loss by making a "double or nothing" response that can either eliminate the previously incurred punishment or double it (50 % probability).

Related to loss-chasing in gambling is the phenomenon of win chasing, which describes the perpetuation of further gambling following a win (Banerjee et al., 2023). A behaviour akin to win chasing has been modelled in rodents using an operant adaptation of the human balloon analogue risk task (BART) (Lejuez et al., 2002; Jentsch et al., 2010). In the rodent BART, rats are presented with two levers, one of which responding upon adds to a cache of potential food reward (i.e., the "add" lever). Responding upon the other lever delivers the food cache for the rat to collect (i.e., the "cash out" lever). Each response on the add lever increases the probability that the next response will result in forfeiture of the entire cache, yet some rats continue to respond upon the add lever within a trial beyond what is optimal for maximum within-session gains, thereby reflecting the construct of win chasing. Interestingly, there appears to be a heritable component to the propensity to win chase in the rodent BART (Ashenhurst et al., 2014).

While the psychological processes involved in the persistence of responding following losses and/or wins remain to be elucidated, animals may be driven impulsively to respond on the "double or nothing" or "add" levers in the rLCT and rodent BART, respectively, by negative or positive urgency, (i.e., an emergent emotional state with highly-polarized valance that drives impulsive behaviour). Indeed, negative and positive urgency have been suggested to play a role in GD as well as in SUD and other compulsive disorders (Cyders and Smith, 2008; Zorrilla and Koob, 2019; Quintero et al., 2020; Fouyssac et al., 2022).

3.2. *Elements of real-world gambling in contemporary animal models*

3.2.1. *Probabilistic uncertainty*

As discussed already, most of the existing preclinical behavioural assays of GLB in animals assess some form of probabilistic decision-making or well-established instrumental performance under probabilistic reinforcement. For instance, in between-session rGT procedures (Zeeb et al., 2009; Barrus et al., 2015), rats possess a schema regarding how likely it is that they will win with each probabilistic option. In these between-session rGT procedures, the probabilistic outcomes remain static over time (within and between sessions) and become unequivocally expected. As such, decision-making in the context of these animal models occurs under conditions of "expected uncertainty" (Yu and Dayan, 2005), where the probability of winning is known. While the probabilities do change over time in the blackjack task and RDT, this is signalled by an explicit discriminative cue or the passing of time, respectively, and as such, the current probabilities are still known to the rat.

In contrast, most real-world gambling occurs under conditions of ambiguity, where the probability is volatile, preventing the player from accurately predicting the odds of winning on the next play. The difference between these two types of uncertainty is not semantic. It has critical ramifications for the shaping of behaviour and implies the engagement of distinct neural systems and computations (Soltani and Izquierdo, 2019). This difference also brings into question whether between-session rGT procedures would have the same predictive validity for GD as the IGT, because the latter has a single trial design, where the participants are initially unaware of the probabilistic nature of each deck, and therefore better incorporates the ambiguity of real-world gambling. Human tests of decision-making under expected uncertainty are not predictive of problem gambling, unlike those testing in conditions of ambiguity (Brevers et al., 2012). To bring the rGT closer to the IGT, Rivalan and colleagues (Rivalan et al., 2009) developed a

single-session version of the rGT in which the contingencies of each probabilistic option were not first learned during the training phase. There is emerging evidence that poor performance in the single version of the rGT, the behavioural pharmacology of which is being progressively characterised, is associated with addiction-relevant behaviours (Daniel et al., 2017; Cocker et al., 2020).

3.2.2. Gambling cues

Modern casinos and the EGMs within exude a sensorily frenzied atmosphere of bright flashing lights and complex sounds that produce a high appetitive arousal state, which draws people in, makes them want to gamble, and keeps them gambling for long periods, leading to a complete immersion in the environment and the games (Dowling et al., 2005; Dixon et al., 2014b). These salient audiovisual stimuli are thought to increase the addictive potential of gambling and have indeed been shown to do so both in the crGT and its human laboratory analogue (Barrus et al., 2016; Barrus and Winstanley, 2016; Cherkasova et al., 2018, 2024).

In addition to their ability to induce arousal, which contributes to the engagement with and the perpetuation of gambling activities, these stimuli are also thought to play an important role in the development of GD through Pavlovian motivational control of behaviour. Through Pavlovian association with the reinforcers of the gambling experience (e.g., monetary wins, excitement, etc.), these stimuli may become either occasion setters or conditioned stimuli (CSs), acquiring motivational salience. Critically, some CSs are response-produced, thereby acting as conditioned reinforcers, which can invigorate and perpetuate instrumental behaviours for long periods of time, even when the outcome is devalued (Colwill and Rescorla, 1985; Parkinson et al., 2005). The biobehavioural nature of the influence of such cues on gambling-like behaviour has not been investigated in any of the behavioural procedures discussed above. This is in marked contrast with the wealth of knowledge gained both from clinical and preclinical research on the influence of drug-paired CSs on drug-related motivational states (subjectively reported as craving by humans), including negative urgency (Fouyssac et al., 2021), and drug-seeking and taking/use in humans with a SUD and rodents.

Craving refers to the subjective report of an affective state where the desire, longing, or urge for a goal or a behaviour associated with previous experiences of reward, relief or anticipatory arousal (be it appetitive or aversive, such as the drug itself or avoidance of withdrawal in the context of SUD (Sinha et al., 2000)) reaches some “subjective threshold of intensity” (Kozlowski and Wilkinson, 1987). Craving, which is now a diagnostic criterion for SUD (American Psychiatric Association, 2013), has been shown to be the most proximal cause and a strong predictor of drug use relapse in humans with a SUD (Vafaie and Kober, 2022). While it is not yet a diagnostic criterion of GD (American Psychiatric Association, 2013) or a common feature of gambling severity scales, craving has been associated with multiple aspects of GD (Mallorqui-Bague et al., 2023). While it is not yet clear whether craving plays as critical a role in GD as it does in SUD, it is not necessarily money that individuals with GD report craving for. As we discuss below, it is often the gambling behaviour itself that they crave.

In humans with SUD, drug craving is measured using various scales and subjective reports that invariably ask the individual how much they want the drug (Mezinskis et al., 2001). In addition, the perceived intensity of an affective state and its labelling, which are highly subjective, vary greatly between individuals, rendering a quantitative analysis of craving very difficult if not impossible (Tiffany et al., 2000). Thus, in spite of the recent discovery of a neuromarker of craving in humans (Koban et al., 2023), it “is an unobservable entity that is not completely reducible to observable events” (Katz and Higgins, 2003). It is, therefore, not yet possible to quantify craving based on behaviour, not even in humans.

While cue-induced craving can obviously not be studied in species devoid of language, the control exerted by CSs and conditioned reinforcers over behaviour, including gambling-like behaviour, can. We later propose a theoretical framework as to *how* these CSs may promote the development of GD. At present, we will address the validity of how gambling-like CSs are featured and interpreted in the contemporary suite of animal models, focusing on the crGT.

3.2.3. Psychological and neural mechanisms of behavioural control by cues in non-human gambling tasks

Despite their omnipresence in modern casino and online gambling, and their putative pro-addictive role in GD, gambling-inspired salient audiovisual cues have only been experimentally investigated in about 6 % of the studies on GLB indexed on PubMed. This dearth of research is not trivial, because the behavioural pharmacology of the crGT differs from that of the uncued version of the task (Winstanley and Hynes, 2024). The lack of attention paid to the role played by cues in preclinical GD research may, together with the limitations of models developed so far, have contributed to the poor translational track record of the field.

To overcome this limitation, it is paramount first to establish experimentally if the cues presented in the crGT act as occasion setters (i.e., discriminative stimuli) or, instead, as CSs, as has been loosely suggested (Adams et al., 2017; Ferland et al., 2019). Even though individuals prone to ascribe incentive salience to CSs (i.e., sign-trackers) choose the riskiest and most highly-cued options in the crGT (Swintosky et al., 2021), it has not yet been demonstrated that their behaviour is influenced by the Pavlovian motivational effects of the cues. Critically, delivery of these cues is contingent on the performance of an operant response, suggesting they may become conditioned reinforcers (CRfs), which are known to be critically important in SUD and GD (e.g., money). In animal models of compulsive drug seeking, CRfs mediate the development of engrained habits that can drive the transition to compulsive drug seeking (Belin and Everitt, 2010; Belin et al., 2011; Everitt et al., 2018). CRfs can invigorate instrumental behaviour while bridging delays to reinforcement but, unlike CSs, they are not tied to the value of their associated unconditioned stimulus (Parkinson et al., 2005). CRfs can therefore influence motivated behaviour independently of the outcome, and (as discussed later) may be part of the reason that people keep gambling despite rarely winning.

In the crGT, the number of response-delivered cues is proportional to the riskiness of each option, such that the worst probabilistic choice delivers the most cues. These contingencies may bias responding towards risky options because they provide the most conditioned reinforcement. Ferland and colleagues made a first attempt to test this hypothesis. They showed that the level of responding for CRfs did not differ between risk-prone and risk-averse individuals, and that it was not influenced either by the presence or absence of cues during rGT training (i.e., rGT vs. crGT) (Ferland et al., 2019). However, responding for CRfs was assessed in a separate test from the rGT/crGT, using CSs that were qualitatively different from those of the gambling task, thereby preventing the assessment of the conditioned reinforcing properties of the gambling task stimuli themselves. Doing so would have required assessing the ability of the task-related cues to support a new instrumental response in rGT/crGT-trained rats.

Even though the other gambling tasks discussed here were not expressly designed to test the effect of casino-like cues on behaviour, the motivational properties of the cues they do feature may still influence behaviour. For example, the odds-signalling discriminative stimuli of the blackjack task could acquire Pavlovian excitatory or inhibitory value, bringing into play the mechanism of discriminative control of instrumental behaviour (Kruse et al., 1983; Colwill and Rescorla, 1988). In this case, behaviour in the task would not only be influenced by cue-informed knowledge of the contingencies, but also by cue-evoked incentive motivational processes. The RDT, rSMT, and rLCT also all feature some form of discrete or contextual cues that could acquire some motivational or discriminative value with the potential of affecting behaviour, all of which could provide new insights into the modulatory effect of cues over gambling-like behaviour.

In summary, we know very little about the role played by cues in the individual differences in risk-proneness observed in gambling tasks in non-human animals, highlighting a ripe line of inquiry on the road to translation. This may be particularly relevant considering the particular influence CSs have over habits as opposed to goal-directed behaviours and the role habits are considered to play in compulsive disorders (Robbins et al., 2024).

3.2.4. Habits

Most new instrumental behaviours are goal-directed, underpinned by action-outcome representations (A-O). Thus, motivated actions are initially initiated under the control of the knowledge of the relationship between the action and its ensuing outcome alongside that of the value/utility of that outcome (e.g., money, in the case of recreational gambling). When such instrumental behaviour is frequently repeated, and the outcome is delivered under schedules of reinforcement that preclude A-O representations, and/or when environmental conditions draw attention away from the behaviour, habits supersede (Thorndike, 1927; Dickinson, 1985; Bouton, 2021).

Habits are stimulus/setting-bound instrumental responses underpinned by covert stimulus/setting-response associations, which are stamped in by the response-produced outcome. Thus, unlike goal-directed behaviours, the enactment of which is preceded and determined by a representation of the utility of the outcome, habitual responses are enacted automatically in the presence of the setting to which they are bound. Any change/update in the strength of the S-R association, and hence the modulation of a habit, is instead dependent on the experience of the S-R-mediated response-produced outcome when its motivational value has changed. Consequently, habits do not differ from goal-directed behaviours under reinforcement or extinction. Instead, while changes in the utility of the outcome, irrespective of how (contingently or not) or where they are experienced, have an immediate consequence on whether the next goal-directed action is initiated and/or its vigor, the same is not the case for habits. Habits are characterised by a relative persistence of responding despite contingency degradation or outcome devaluation, for as long as the organism does not experience the devalued outcome upon responding [i.e., as long as it is tested under extinction conditions (Robbins and Costa, 2017)]. The difference between actions and habits, therefore, lies in the psychological and neural mechanisms that control the initiation of a behavioural sequence, not its performance under reinforcement.

In the case of GD, the focus should, therefore, not be on the associative nature of the behaviour during a gambling bout (performance) but rather on the mechanisms that underlie the initiation of gambling. While the extent to which engaging in adaptive or compulsive gambling in humans or animals is habitual remains to be fully investigated, it is easy to see parallels between the well-defined conditions that promote habits and the modern gambling environment. Because habits are covert processes, they may be more conducive to loss of control than overt goal-directed behaviours. It is perhaps unsurprising, then, that even though widely ignored, habits have long been suggested to play a role in the development and progression of GD (Dickerson, 1993; Griffiths, 1993a; Boffo et al., 2018; Ferrari et al., 2022), especially via interactions with gambling cues (Brevers et al., 2019; Wyckmans et al., 2019).

The potential relationship between the individual tendency to exhibit habitual responding and GLB has been explored in the RDT, rGT, and crGT (Zeeb and Winstanley, 2013; Gabriel et al., 2019; Hathaway et al., 2021). Rats with a greater propensity to switch to habitual responding in an instrumental task separate from the RDT were shown not to be more prone to engage in risky decision-making in the RDT (Gabriel et al., 2019). However, this study was designed on the assumption that the tendency to develop habitual responding in a specific context for a given reinforcer generalises to another task in another context. In marked contrast, habits, by virtue of their nature (i.e., they are stimulus-bound), are extremely sensitive to context shifts (Thrailkill and Bouton, 2015; Bouton, 2021). Most importantly, the tendency to readily develop habits does not reflect an increased vulnerability to developing compulsive behaviours (e.g., persisting in engaging in a behaviour in the face of adverse consequences), as habits are usually highly adaptive. Instead, it is the inability to relinquish habits in the face of changes in the environment that render them maladaptive and contributes to compulsion (Belin et al., 2013; Everitt and Robbins, 2016; Giuliano et al., 2019).

3.2.5. Modelling loss

A hallmark feature of all real-world human gambling is the high likelihood of experiencing financial loss, which is associated with, or even the cause of, a high level of anticipatory arousal (Sharpe, 2004). There are also long-term negative consequences of gambling loss, such as the loss of relationships, social status, employment, etc. Such long-term losses from gambling are, in essence, a form of negative punishment. As such, the negative consequences associated with GD come categorically and arguably predominantly in the form of negative punishment, that is, punishment due to a response-produced loss of an otherwise rewarding outcome. The use in rodent GLB tasks of positive punishment (where the response produces a new, inherently aversive, outcome) may not be the most translationally valid approach to assess the compulsive nature of gambling in non-human animals. So, while the RDT (Simon et al., 2009) and the early precursor to the rGT that signalled loss with quinine-tainted food (van den Bos et al., 2012) provide valuable insights into the role of positive punishment in decision-making, such tasks may not capture the psychological mechanisms involved in human gambling as well as the rGT, crGT, rSMT, rLCT, and the blackjack task the losing trials of which all feature losses of opportunity to obtain reward in the form of time-out punishments (Zeeb et al., 2009; Winstanley et al., 2011; Barrus and Winstanley, 2016; Floresco et al., 2018). These time-outs are a measurably aversive mode of negative punishment in numerous experimental non-human species (Leitenberg, 1965). Opportunity costs, however, are still not equivalent to the out-of-pocket (i.e., explicit) losses or total bankruptcies that often occur in real-world gambling, with the latter being heavily overweighted in economic decision-making (Kahneman and Tversky, 1979; Thaler, 1980; Weber and Welfens, 2011). Signalling an out-of-pocket loss to a non-human animal presents a difficult challenge that has yet to be surmounted, with a perhaps even more challenging issue arising from the need to signal an analogue of the immense loss that arises from complete bankruptcy. The answer to how losses akin to those experienced in real-world human gambling may be incorporated into an animal model lies in understanding the psychological mechanisms and affective states that such losses evoke and the behavioural sequelae thereof. One potential avenue is to give the animal occasionally a very high-yield choice accompanied by the risk of a massive loss, say, all the food they may have earned during the session.

3.2.6. Psychological mechanisms of loss-chasing

While losses are aversive to the average individual, they occur more frequently than wins in gambling, yet the frequency of play still increases over time. Knowledge of the psychological processes that underlie this apparent paradox may contribute to our understanding of the phenomenon of loss-chasing, a core psychological element of GD. Individuals with a GD exhibit altered affective and neural responsivity to loss (Brevers et al., 2012; Gelskov et al., 2016; Genauck et al., 2017), as well as a reduced ability to use information about loss magnitude to adaptively guide future decision-making (Limbrick-Oldfield et al., 2021). Such altered responsivity to loss is also evident in risk-preferring rats in the rGT, which, as revealed by an elegant computational approach, show altered learning from time-out punishments (Langdon et al., 2019). Despite the resounding evidence that losses are processed *differently* in individuals with GD and risk-preferring rats, this falls short of explaining the active chasing of losses, the psychological and neurobehavioural mechanisms of which are not fully understood. One hypothesis is that losses generate negative urgency, which promotes

excessive gambling in GD (Zhang and Clark, 2020). Negative urgency is a negative emotional state that causes individuals to act impulsively or compulsively engage in behaviours that are fraught with negative consequences, the experience of which contributes to craving and relapse in SUD (Cyders and Smith, 2008; Um et al., 2019; Zorrilla and Koob, 2019; Fouyssac et al., 2022) and the severity of GD (Cyders and Smith, 2008; Zorrilla and Koob, 2019; Quintero et al., 2020). In animal models of gambling, denying the opportunity to engage in gambling-like behaviour via time-out punishments could likewise evoke a state of negative urgency that promotes further gambling-like behaviour as has been shown to be case for incentive drug-seeking habits (Fouyssac et al., 2022).

As discussed above, in GD the goal (or perceived motivation) for many seems no longer to be winning money per se but rather to engage in the act of gambling itself. Such a shift in the motivation for a goal object to the motivation to engage in the behaviour itself, which subjectively may be manifested as a shift from 'I want' to 'I must', has been suggested to represent a feature of compulsive behaviours (Robbins et al., 2024). As such, over the course of the development of GD, monetary losses should become progressively less distressing and lose their power to evoke negative urgency. Positive urgency may play a more prominent role at this stage, whereby positive affective states rouse the impulsive and compulsive tendencies to gamble (Cyders and Smith, 2008). Instead of bringing about negative emotions, losses in GD may conjure a state of positive anticipatory arousal, because they signal the opportunity for subsequent gambling. Such anticipatory arousal could set in motion the mechanism of positive urgency (i.e., a positive emotional state that evokes impulsivity) and cause individuals to gamble more. The role of positive and negative urgency in loss-chasing over the course of the development and the expression of GD and GLB is an area for future research within the framework of the three subtypes of vulnerably to develop GD: type 1, driven by reward, type 2, driven by avoidance of negative internal states and type 3, driven by high impulsivity (Milosevic and Ledgerwood, 2010).

3.2.7. *Impulsivity*

The ability of negative and positive urgency to invigorate gambling hinges partially on their ability to promote harsh behaviours, or impulsive decisions and actions (Dalley and Robbins, 2017; Halcomb et al., 2019). Impulsivity, which is a multifaceted latent marker of vulnerability to develop several compulsive behaviours across species (Robbins et al., 2012), is also a prominent feature of GD (Hodgins and Holub, 2015; Ioannidis et al., 2019; Mestre-Bach et al., 2020). It is therefore unsurprising that understanding the psychological, neural and cellular mechanisms through which impulsivity contributes to GD has been identified as a critical research priority in the UK (Bowden-Jones et al., 2022). Animal models with heuristic value with regards to the human condition, such as a high impulsivity trait as assessed in the 5-choice serial reaction time task (Robbins, 2002), which operationalises motor impulsivity, have historically been of great utility in behaviourally parsing the components of impulsivity and their disparate neurobiological substrates (Dalley and Robbins, 2017). Because the rGT/crGT tasks are structurally derived from the 5CSRTT, they enable, in some specific circumstances, the simultaneous assessment of motor impulsivity and risky decision-making tendencies. This has led to the discovery that male rats that exhibit high levels of motor impulsivity are also prone to risky decision- making, and that chemogenetic manipulations that decrease the latter do so by reducing the former (Barrus et al., 2015; Hynes et al., 2021). Motor impulsivity is also correlated with risk-taking in the RDT (Gabriel et al., 2019), but because the RDT is devoid of built-in capacity to measure motor impulsivity, it remains to be established whether motor impulsivity mediates risky decision-making in this task. These observations together lend support to the hypothesis that gambling-adjacent decision-making and motor impulsivity share some common latent construct, the neurobiological nature of which can be deciphered using procedures such as the rGT/crGT. Thus, task-concurrent assessment of various facets of impulsivity (Evenden, 1999) should be a structural element of any translationally relevant animal model of GD.

4. A psychological framework for gambling disorder: a novel application of the incentive habit theory of compulsion

GD is the only non-substance-related disorder to be included in the DSM-5 section of substance-related and addictive disorders, emphasizing that GD, AUD and SUD are behavioural disorders that share many common phenomenological, psychological, (Leeman and Potenza, 2012) and neurobiological (Potenza, 2008) features. At the core of all these disorders lies compulsion (Robbins et al., 2024). However, there are some important differences. For example, in SUD and AUD, there can be direct and sometimes toxic pharmacological effects of drugs on the brain (with the potential to impact current decision-making), whereas it seems reasonable to assume that this is not the case with gambling itself. Despite some divergence in the structural and functional correlates of GD and AUD, as revealed by brain imaging in humans (Clark et al., 2019), GD is nonetheless highly comorbid with AUD or SUD (Petry and Pietrzak, 2004; Grant and Chamberlain, 2020).

Such overlap between GD and AUD/SUD is further supported by intriguing interactions between GLB and the self-administration of both cocaine and opioids (Ferland et al., 2019; Hynes et al., 2021, 2024b; Wheeler et al., 2023), bringing to light the possibility that existing theories of drug addiction may jointly provide an interesting framework for the understanding of the psychological and neural basis of GD [i.e., incentive sensitization (Robinson et al., 2016; Hellberg et al., 2019), hedonic allostasis (Koob and Le Moal, 2001; Zorrilla and Koob, 2019), aberrant positive reinforcement (Wise and Robble, 2020), and compulsive incentive habits (Belin and Everitt, 2010; Belin et al., 2013; Robbins et al., 2024).

4.1. *From positive to negative reinforcement: the transition from recreational gambling to GD*

Positive reinforcement, largely from actual monetary gain, which recruits positive anticipatory arousal states, plays a larger role in recreational gambling than it does in GD (Weatherly and Derenne, 2012; Weatherly et al., 2012) (Fig. 2**A**). While recreational gamblers often gamble to win and/or have fun, those with GD receive diminishing/-reduced positive reinforcement from those elements of the experience in which they keep engaging. Gambling in individuals with GD is more frequently motivated by negative reinforcement, where gambling is a means of numbing or maladaptively coping with negative emotional states (Neophytou et al., 2023), such as those associated with stress, exogenous depression, and anxiety, either due to intrinsic alterations in emotion regulation predating the onset of GD (Williams et al., 2012; Thurm et al., 2023) or the incurrence of gambling-induced financial or social loss (Wood and Griffiths, 2007; Weatherly et al., 2010) (Fig. 2**B**). It seems conceivable that the perpetuation of gambling may be partially rooted in the development of gambling-induced "hyperkatifeia" (i.e., hypersensitivity to emotional distress) that the individual with GD tries constantly to 'self-medicate' by engaging in more gambling, similar to how negative reinforcement contributes to the perpetuation of drug seeking and drug use in SUD or AUD (Koob, 2022).

Even though deficits in emotion regulation strategy may promote the engagement in gambling as a coping strategy, negative reinforcement alone does not seem sufficient to explain the compulsive nature of the behaviour in individuals with GD, no more than it does in those with AUD or SUD. Importantly, the motivational salience of gambling-related paraphernalia and cues, has long been shown to promote gambling behaviour.

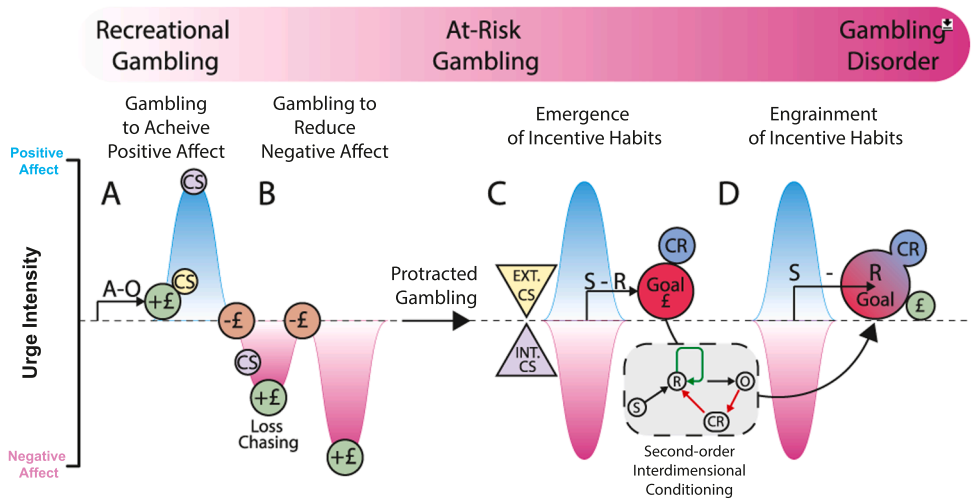


Fig. 2. Psychological mechanisms underlying the transition from recreational gambling to gambling disorder. (A) Recreational gambling starts as goal-directed [i.e., under action-outcome (A-O) control]. Recreational gambling is initially maintained in most by positive reinforcement, with the goal being winning money, even though in some it may be a way to cope with stress or negative emotions. (B) As losses accumulate, negative reinforcement tends to play a larger role and gamblers may engage in loss chasing to recuperate losses or to escape from the negative emotions that result from losses. Exteroceptive cues such as those emitted from gambling machines and interoceptive cues such as the somatic states arising from winning or losing become conditioned stimuli (CSs). (C) In some individuals, protracted gambling causes a transition from A-O control to stimulus-response (S-R) control of behaviour. Interoceptive or exteroceptive CSs can spur positive or negative arousal states that enact an S-R behavioural sequence that contributes to persistent gambling despite negative consequences for life. (D) Incentive habits become engrained when the CSs produced by gambling (e.g., machine-emitted cues or positive arousal states) become conditioned reinforcers (CRs) that drive second-order pavlovian to instrumental interdimensional conditioning to imbue the gambling behaviour itself with the incentive motivational value of the CR. The goal has now become to simply engage in gambling itself.

4.2. *Incentive sensitization*

The "incentive sensitization" theory of addiction (Robinson and Berridge, 1993), which focuses on appetitive Pavlovian motivational mechanisms, offers a potential framework to understand the control that these gambling-related cues have over behaviour. This theory posits that the CSs associated with drugs of abuse (e.g., a crack pipe or syringe) gain aberrant and ever-increasing incentive value with continued use from the first exposure onwards due to a drug-induced sensitisation of the response of dopamine neurons to these cues following repeated exposure. The theory furthermore suggests that encountering such cues during periods of abstinence can evoke a craving for the drug that is sufficient to cause relapse. It has been suggested that gambling cues may also acquire incentive motivational value (Goudriaan et al., 2014; Barrus et al., 2016; Hellberg et al., 2019; Anselme and Robinson, 2020; Robinson et al., 2022). Upon recurrent experiences of dopamine-dependent appetitive anticipatory states associated with the reinforcing properties of the gambling experience, the incentive motivational value of these gambling CSs may sensitise, thereby enabling them to goad individuals toward the cue-emitting casinos and the gambling apparatus therein (Robinson et al., 2016). While the incentive sensitization theory can partially account for why individuals may relapse to gambling after a period of abstinence, it fails to explain why only some individuals with an experience of gambling, or indeed drug use, actually lose control over their behaviour and switch to compulsion. The incentive sensitization theory also fails to explain why, once those with GD begin a session of gambling, they are so immersed that they cannot disengage from the game, despite incurring losses that dramatically impact their quality of life. Just as it does with drug addiction, the incentive sensitization theory falls short of explaining the most psychiatrically relevant facet of pathological gambling – habitual and compulsive engagement.

4.3. *An incentive habit theory of GD*

What, then, could explain the phenomenon of perpetually re-engaging in gambling behaviour despite its negative consequences? Some patients refer to the experience of gambling as being perceived as "trance-like"(Schüll, 2012b) and automatic, which can mean losses may not be fully appreciated in the moment. In the context of gambling, the latter cognitive-behavioural phenomenology has been called the gambling "zone" or "dark flow" (Partington et al., 2009; Schüll, 2012a; Dixon et al., 2014a), but such conceptualizations are largely descriptive and do not hone in on the basic behavioural mechanisms that produce the pathological gambling behaviour.

One potential theoretical framework that accounts for the compulsive and immersive nature of gambling in individuals with GD is the incentive habit theory, initially applied to SUD (Belin and Everitt, 2010; Belin et al., 2011, 2013). Formally, this theory posits that conditioned reinforcement enables the transfer of the motivational value of response-produced external or internal CSs or discriminative stimuli (DSs) to instrumental responses with value-free representation [e.g., stimulus-response (S-R) habits]. This transfer, which imbues the response with motivational value, is suggested to be mediated by the CRf through a Pavlovian (US-CS/DS) to Instrumental (S-R-CRf) second-order interdimensional conditioning process (Belin et al., 2009) (Fig. 2**C & 2D**). In the context of GD, this enables the incentive motivational value of CS/DSs associated with the appetitive anticipatory arousal related to the prospect of Gambling, and those associated with the transient relief of negative affective states brought about by engaging in gambling behaviour, to permeate the S-R association that underlies habitual responses. Thence that response, otherwise elicited by either positive or negative affective states and their associated CS/DSs, acquires motivational and reinforcing properties (Robbins et al., 2024). Consequently, in the absence of any representation of the outcome of a gambling bout, an individual with a GD will engage in a behavioural sequence that will eventually lead to gambling, in response to stimuli (exteroceptive, cognitive, or interoceptive) to which gambling is bound. But most importantly, the mere thought of gambling, or withdrawal from it, can generate a motivation, mediated by either positive or negative urgency, respectively, to enact the behavioural response: it is the behaviour itself that is craved, not financial gain, as so often reported by individuals with GD.

When associated with impairment of top-down executive control,

manifested, for instance, as high trait impulsivity, these processes may cause some individuals to lose control over incentive gambling habits and develop GD, just as such impairment has been shown relevant in the context of SUD (Giuliano et al., 2019; Fouyssac et al., 2022; Jones et al., 2024).

Contemporary gambling settings are highly conducive to the development of incentive habits. The random schedules of reinforcement in gambling are the most effective schedules in strengthening habitual behaviour (Mowrer and Jones, 1945), partially explaining why gambling behaviour rapidly becomes habitual. Moreover, the many response-produced salient win-concurrent audiovisual cues of the modern casino environment are by their temporal association with monetary reward, well-positioned to acquire conditioned reinforcing properties. It is not only following the wins that audiovisual cues are emitted, however. Both plays that deliver less than was originally wagered (i.e., "losses disguised as wins") and those that are outright losses but designed to suggest an imminent win (i.e., near-misses) also deliver similar or identical cues to that of proper wins, which through stimulus generalization become CRfs too (Daly et al., 2014; Belisle and Dixon, 2016). Thus, the entire audio-visual milieu of the electronic gambling machine is somehow designed to facilitate the control of CRfs over behaviour, maintaining gambling by essentially bridging the delay between the relatively rare episodes of primary reinforcement (i.e., monetary wins). In the case of acute proper losses, where neither primary nor conditioned reinforcement is present, further gambling behaviour may be produced through negative or positive urgency.

Gambling cues may enhance the vigour and frequency of incentive habit-mediated gambling through a process known as Pavlovian-to-instrumental transfer (PIT) (Estes, 1948; Lovibond, 1983). The classically conditioned incentive motivational value of gambling cues imbues them with the ability to powerfully affect instrumental gambling behaviour even when presented non contingently upon responding. For example, once an individual sits in front of a slot machine and starts playing, the cues stream in, and potentially elicit PIT, which may result in an explosion in the motivation to play more and play faster. The increase in the vigour and speed of behaviour is a characteristic property of instrumental habits (Smith and Graybiel, 2014). Indeed, people with GD demonstrate more pronounced PIT than recreational gamblers in a laboratory setting (Genauck et al., 2021; Xu et al., 2024).

As previously discussed, even the most ingrained habits will extinguish if the primary reward is withheld for long enough (Mowrer, 1943; Dickinson et al., 1995; Bouton, 2024), but just the opposite is observed in pathological gamblers, who continue to play in the absence of wins, and even despite encountering desperately long losing streaks. How could this be? An *incentive* gambling habit theory (Fig. 2) can be postulated to explain why individuals with GD persist in gambling irrespective of the immediate outcome of their gambling: the behaviour has become self-reinforcing, and it is the associated anticipatory arousal state that is sought by the gambler. Thus, an incentive gambling habit theory provides a framework for a rather insidious pro-addictive biopsychological mechanism for GD, relying on the ability of gambling cues (1) to maintain play despite rewards being scarce, (2) invigorate the frequency and urgency with which individuals gamble, and (3) render the physical act of gambling rewarding in and of itself (Robbins et al., 2024).

Since incentive drug-seeking habits have been successfully shown to contribute to the transition from controlled to compulsive cocaine (Fouyssac et al., 2022; Jones et al., 2024), alcohol (Giuliano et al., 2021), and heroin (unpublished) seeking in rodents, they are a promising candidate for operationalization in the next generation of animal models of GD.

5. Recommendations for a translationally effective approach to animal experimentation on gambling-like behaviour

Integrating the concepts discussed above with the literature, we propose a list of features that next-generation gambling task(s) should include:

1. **Moving beyond reinforcement- and craving-based operationalization and shifting focus to incentive habits.** The addiction-relevant implications of observations from animal models of GD have primarily been interpreted through the lens of positive/negative reinforcement and incentive sensitization theories of addiction; these theories alone are insufficient to explain the emergence of the compulsive gambling habits that are observed in GD. The design of future animal models should be amenable to the inference of behavioural phenomena that are promoted by incentive habits, such as negative urgency-mediated relapse to the seeking of an opportunity to gamble (i.e., gambling seeking), in line with a recent demonstration of this mechanism in the context of SUD (Fouyssac et al., 2022). Gambling seeking could be operationalised using a heterogenous seeking-taking chain schedule of reinforcement similar to that used in models of drug-seeking (Vanderschuren and Everitt, 2004), where animals would press a seeking lever for a relatively long period of time to access the opportunity to gamble. Of particular relevance to operationalizing incentive habits would be to reinforce the seeking response by response-produced stimuli associated with gambling (i.e., conditioned reinforcers). A prediction in support of the development of incentive habits would be that animals would engage in seeking even when the opportunity to gamble is transiently lost and they would display rebound in gambling seeking when given the opportunity to press on the seeking after periods of forced or volitional abstinence, as is the case for incentive cocaine seeking habits (Fouyssac et al., 2022).

   As with alcohol, cocaine, heroin, and compulsive coping behaviour (Belin and Everitt, 2008; Giuliano et al., 2019; Hodebourg et al., 2019; Marti-Prats et al., 2023), incentive habit-derived gambling seeking should also come under the control of anterior dorsolateral striatum (aDLS) dopamine-dependent mechanisms. A further prediction of an incentive habit theory of GD is, therefore, that intra-aDLS dopamine receptor antagonism would suppress gambling seeking but not gambling performance.
2. **Embedding the Pavlovian and instrumental mechanisms underlying the pro-addictive and/or incentive habit-promoting power of Pavlovian-instrumental interactions.** Gambling cues are a feature of modern gambling with important psychological implications in terms of the facilitation of pathological gambling behaviour (Dowling et al., 2005; Dixon et al., 2014b). Cue-related processes may, therefore, be a fruitful target for therapeutics, yet the existing suite of GLB tasks does not sufficiently probe the influence of gambling-like cues on behaviour in a gambling setting (e.g., conditioned reinforcement and PIT). The translational prospect of animal models of gambling-like behaviour will be substantially improved by the development of tasks that yield a granular picture of cue-related psychological mechanisms.
3. **Exhibiting predictive validity for putative treatments.** A vast repertoire of pharmacological (Simon et al., 2011; Barrus and Winstanley, 2016; Cocker et al., 2019; Betts et al., 2021), chemogenetic (Hynes et al., 2020, 2021, 2024b; Arrondeau et al., 2024), and optogenetic (Orsini et al., 2017; Bercovici et al., 2018) manipulations have been shown to reduce GLB in non-human mammals, yet none of these putative or potential therapeutic interventions has, or can be, at least yet, translated into the clinic. Conversely, the drugs effective in treating GD do not appear to affect risky, sub-optimal decision-making in the current GLB tasks (Di Ciano and Le Foll, 2016; Tjernstrom and Roman, 2022). It will be necessary to validate the next generation of animal models of GD by ensuring their responsivity to existing therapeutic strategies that are at least partially effective in humans, such as naltrexone.
4. **Merging decision making under ambiguity with opportunities to really gamble.** The majority of existing animal models of

gambling-like behaviour assess decision-making under expected uncertainty. Such conditions do not accurately model the type of probability encountered in real-world gambling, nor are human tests of decision-making under expected uncertainty predictive of problem gambling (Brevers et al., 2012). Progress toward a more translational suite of animal gambling models should instead focus on decision-making under ambiguity (Rivalan et al., 2009; Daniel et al., 2017; Cocker et al., 2020). But that will not be sufficient. An animal model of GD will require the individuals to go beyond the maximisation of outcome under ambiguity, and to have to take risks that are biologically significant.

5. **Capturing the compulsive nature of GD.** Persistent gambling in the face of bankrupting financial loss or severe legal and/or social repercussions is a recognisable hallmark and essential diagnostic feature of GD. Incentive habits may represent a conduit for the development of these compulsive gambling behaviours, but identifying individual differences in the tendency to persist in gambling in the face of biologically relevant losses is a unique challenge that has yet to be addressed. Surmounting this challenge may provide the missing link in the pursuit of a translationally effective animal model of gambling-like behaviour. It can be argued that only with such a valid preclinical model of GD will the leverage of cutting-edge neuroscience technology help us gain a mechanistic understanding of the psychological, behavioural, neural, cellular and molecular basis of GD and of the factors that confer individual vulnerability to switch form recreational gambling to compulsive incentive gambling habits.

5.1. Harnessing the power of prospective longitudinal mechanistic studies on large cohorts of outbred rodents to understand the biobehavioural basis of the individual vulnerability to develop GD

The great advantage of preclinical research is the opportunity to characterise, in a well-controlled environment, the behavioural and neural profile (either using brain imaging techniques, or more invasive approaches, such as electrophysiology or fibre photometry) of each individual before and after the development of a compulsive phenotype (Belin et al., 2008; Belin-Rauscent et al., 2016; Jones et al., 2024). This, combined with genetics and causal interrogations of brain systems or circuits and cellular/molecular profiling such as single-cell transcriptomics, could offer groundbreaking insights into the biobehavioural basis of GD.

5.1.1. Neural measurement

While modern neuroimaging (e.g., fMRI, PET, and DTI) may offer some insight into the neurobiological correlates of gambling-relevant behaviours in humans, it is practically impossible to measure brain activity with cell type, neural projection, and/or neurotransmitter specificity in our species. It would also be nearly impossible to monitor brain activity in an ethologically valid way (i.e., while people are engaging in real-world gambling), let alone longitudinally over the course of the development of GD. The use of extracellular multi-array electrophysiology (Song et al., 2024) or *in vivo* fibre photometry (Simpson et al., 2024) in combination with Cre-driver lines or Cre-expressing viruses and neurotransmitter-specific fluorescent biosensors has revolutionized our ability to time-lock neurotransmission to behavioural phenomena, although the use of such approaches has been scarcely adopted in animal models of gambling-like behaviour. Doing so could reveal dynamic neurobiological processes that contribute to the longitudinal development of gambling-like behaviour and inform the identification of novel therapeutics.

5.1.2. Neural manipulation

For the foreseeable future, therapeutics targeting the neurobiological substrates of GD will be largely limited to systemic pharmacology or neurostimulation (Del Mauro et al., 2023), the therapeutic potential of which needs to be further characterised. However, direct intracerebral pharmacological interference, or chemo- and optogenetic manipulation of neural/neurochemical systems and delineated circuits identified by *in vivo* brain recordings could lead to a level of mechanistic understanding of the brain basis of GD that could powerfully inform the development of new treatments. Substantial progress has already been made on this front. Striatal cholinergic interneurons, acetylcholine, and VTA dopamine neurons have been causally shown to gate the development (Betts et al., 2021; Hynes et al., 2021, 2024b; Winstanley et al., 2021) and expression (Hynes et al., 2020) of risky decision-making in the rGT/crGT. Our recent findings that striatal astrocytes mediate the development of incentive cocaine- and heroin-seeking habits (Hodebourg et al., 2019; Hynes et al., 2024a) suggest that non-neuronal brain mechanisms elusive to brain imaging in humans, may also be at play in the pathophysiology of GD. Causal evidence of such involvement relies on the cell-specificity offered by approaches such as opto- or chemogenetics or similar contemporary neuroscience approaches. Another considerable advantage of causal investigations of brain mechanisms in preclinical models of GD is the temporal scale on which the manipulations are conducted. Just as GD emerges over time, on current animal models of risky decision-making, the maladaptive phenotype too emerges and worsens longitudinally. In line with this, chronic pharmacological and chemogenetic manipulations affect gambling-like behaviour more profoundly than the same manipulations do acutely (Tremblay et al., 2019; Hynes et al., 2020, 2021, 2024b; Mortazavi et al., 2023). In addition to being more reflective of how pharmacotherapies are clinically administered (i.e., chronically), longitudinal manipulations in pre-clinical animal models can help elucidate at what time points the various within- and between-systems neural adaptations that drive the disparate behavioural phases of the development of GD occur. It is likely that each unique emergent stage of GD recruits different neural circuits, involves different neurotransmitter systems, and may consequently require a different type of therapeutic intervention.

5.1.3. Genetics

There is emerging evidence that genetic factors play a role in the development of GD (for review, see Warrier et al., 2024), but such studies in humans are necessarily correlational. In rodents, there too appears to be a genetic component to GLB (Ashenhurst et al., 2014; Gabriel et al., 2023), suggesting that causal genetic manipulations may offer great insight into the functional and behavioural consequences of a specific genetic determinant. The gene-protein functional relationship that governs many biological mechanisms does not necessarily apply to the brain in which the same protein can have even opposing roles depending on the cell type, the brain region or the circuit it is expressed in. Developing a brain-wide anatomically specific transcriptomic profile of GD vulnerability is quite prohibitive because the post-mortem brains of individuals with a lifetime history of GD are in limited supply. In contrast, cost effective and scalable platforms like RNAScope™ have made conducting single-cell transcriptomic analysis in rodent brain tissue quite accessible to behavioural neuroscientists. For instance, using this technology, we have recently identified anatomically defined transcriptomic signatures that are associated with several compulsive or incentive habit-related behaviours (Velazquez-Sanchez et al., 2023; Hynes et al., 2024a) and are presently in the process of doing the same for gambling-like behaviour. Once the gambling-relevant genetic candidates and their respective brain regions have been identified, it will be possible to use the CRISPR-Cas9 system to manipulate and understand their *causal* relevance in GLB, thereby achieving a depth of experimental interrogation of the genetic basis of GD that is unequivocally impossible in humans.

5.1.4. Biological sex differences

The prevalence, clinical presentation, vulnerability factors and

biological underpinnings of GD differ between women and men (Slutske et al., 2009; Merkouris et al., 2016; Li et al., 2020; Zhang et al., 2020; Gartner et al., 2022; Estevez et al., 2023), highlighting an imperative consideration for the development of sex-based precision pharmaco- and psychotherapeutics. In human studies, however, the biological factor of sex is necessarily conflated with the socio-political construct of gender (Caplan and Caplan, 2015). Animal models of gambling can therefore be of great utility in this regard, where the contributions of biological sex to differences in GLB and the differential responsivity to interventions across the sexes can be objectively studied while hormonal status is controlled for. Indeed, a nascent body of research has already revealed stark sex differences of both organizational and hormonal contributors to GLB (Orsini et al., 2016, 2022; Hernandez et al., 2020).

6. Concluding remarks

The recent announcement of a statutory tax levy on gambling operators in the UK to support research on GD presents a unique opportunity to invest in the development of a coherent nationwide translational programme of research. A successful research programme relies on a smooth and effective articulation of preclinical and clinical research. The first milestone is the development of a novel, valid preclinical model of GD. In this review, we have outlined the limitations of current animal procedures claiming to operationalise GD, namely economic-based decision-making in the absence of any real biologically relevant gamble. Through analysis and discussion of the psychological and behavioural determinants of GD, several key features have been identified that should be considered in the development of a valid model of GD, including the manifestation of compulsive incentive gambling habits. It is hoped that such preclinical models, once validated, will be useful to improve understanding of neurobiological and contextual factors contributing to GD in humans as well as help to understand treatment efficacy across drug classes, and potentially identify novel pharmacological agents that could be tested in clinical trials, as well as informing psychological processes that could be more optimally targeted via psychotherapy.

Conflict of Interest and Disclosures

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