Animal Models of Gambling-Related Behaviour

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6.1 Introduction

Gambling or wagering on uncertain outcomes is a widespread and pervasive part of society, as estimates suggest that the vast majority of individuals engage in some form of gambling at least once a year [1, 2]. For most, gambling is a relatively harmless pastime, but for some individuals it can become a maladaptive compulsion akin to drug or alcohol addiction resulting in severe impairments in social and occupational functioning and a significantly elevated risk of suicide [3–5].

The recent reclassification of gambling disorder (GD) as an addictive disorder in the DSM-V reflects a growing recognition that the phenomenology underlying both behavioural and substance addictions may best be considered as equivalent (see [6, 7] for review). However, GD could arguably be conceptualised as a 'pure' addiction, in that the behavioural perturbations observed within GD are not accompanied by ingestion of a psychoactive substance. Consequently, a more complete understanding of GD could offer insight into the motivation underlying the commencement of substance addiction, particularly as precipitating vulnerabilities may be obfuscated in drug addicts following the ingestion of psychoactive substances. Problem gambling may therefore offer an ideal platform from which to make inferences about the development of the cycle of addiction, both cognitively and neurobiologically, independent of any changes induced by the pharmacological actions of drugs themselves [8]. However, problematic engagement with gambling in humans is often co-morbid with affective and substance use disorders, making it difficult to

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truly remove confounds relating to drug use and other psychiatric issues when examining behaviour [9]. In this regard animal models may offer a solution, in that they offer an invaluable opportunity to elucidate the underlying neurobiological underpinnings of GD without the issues of causality that are endemic to human research. Animal models with sufficient face, construct and predictive validity may not only aid in a better understanding of GD but also facilitate the development of more efficacious treatment options.

However, whether an animal model can completely encapsulate disease states where the aetiology is likely complex and multifactorial, such as addictive disorders, is unclear. Such a consideration is especially pertinent in the case of GD, given that there are a wide range of gambling games that appeal to demonstrably differing demographics [10]. Consequently, the motivation and the associated neurobiological sequelae promoting the formation and persistence of gambling engagement are likely to be diverse. As such, considering different gambling games as potentially subject to independent expression and regulation, rather than assuming a universal pro-gambling phenotype, may be a more efficacious starting point for exploring risk factors for the development of GD. Moreover, such an approach is in line with emerging diagnostic frameworks [11, 12]. To that end animal models that capture different facets of dysfunction commonly observed in GD may be useful in delineating a conceptual framework of precipitating vulnerabilities towards differing forms of gambling.

A number of factors may contribute to the formation and maintenance of problem gambling in human populations, such as the increased presence of cognitive biases or distorted beliefs regarding the outcome of uncertain events [13, 14], increased levels of impulsivity [15–20], perturbations in cost-benefit decision-making [21–23] and augmented cue reactivity [24–27]. Importantly, all of these processes can be modelled in animals. Therefore, this chapter will initially discuss findings indicating that rats, like humans, are susceptible to cognitive biases that may facilitate continued gambling engagement. Subsequently we will briefly discuss multiple paradigms that can be used to measure impulsivity and touch upon a potential role for increased compulsivity in the development of GD. Relatedly, we will also examine several rodent models of decision-making, wherein perturbations in cost-benefit judgements cannot be attributed to a rise in impulsivity—indicating that these two constructs may represent differing vulnerabilities towards the development of GD. Lastly, we will examine increased cue reactivity and how that might contribute towards problem gambling.

For the sake of brevity, we will restrict this discussion to the use of tasks that utilise rodents, as rodent models have been more widely used for both neural and pharmacological characterisation studies. Moreover, all of the tasks discussed herein utilise computer-controlled operant chambers, as the use of such apparatus minimises inter-experimenter variation and allows for multiple behavioural measurements as well as rigid parameter control through greater automation. All the tasks discussed here can be run in standard five-hole operant chambers. These chambers contain an array of five response apertures on one wall, each fitted with an infrared beam capable of detecting nose-poke entries. Along the opposite wall, two retractable levers or other manipulanda can be installed, typically positioned on

either side of a food tray into which sugar pellets are delivered via an external dispenser. The paradigms discussed herein are not intended as an exhaustive list, but simply highlight a number of tools that may be beneficial in providing a quantitative measure of several facets of gambling-related behaviour.

6.2 The Rodent Slot Machine Task

There are numerous forms of cognitive biases or distortions within gambling; indeed these perturbations are not only used to probe the severity of problem gambling, but their continued presence following treatment can reliably predict relapse [28–31]. Broadly it appears that rats, like humans, are susceptible to similar biases and distortions (see [32] for a more complete discussion of these biases). Here we intend to focus on one particular distortion that is modelled using the rodent slot machine task (rSMT). Behaviour on the rSMT has consistently demonstrated that the presence of multiple reward-related stimuli presented within a compound stimulus array generates the expectation of future reward [33]. Put more simply, rats like humans appear susceptible to the near-miss effect. Near-misses are unsuccessful outcomes that are visually proximal to a win, such as matching two out of three items on a slot machine payline. Subjectively near-misses are experienced as aversive [34], but these sorts of trials reliably promote continued game play, fostering beliefs of mastery and that winning outcomes are imminent [35–37]. Near-misses have garnered considerable attention as a cognitive distortion in human gamblers and have been suggested to make a key contribution to the particularly virulent form of gambling often associated with slot machines and other electronic gaming machines (EGMs) (see [38] for discussion). EGMs such as slot machines are often reported as the primary game of choice by patients presenting for treatment for GD, and these individuals also show the shortest latency between the onset of recreational play and the development of problematic engagement [39–41].

Imaging studies have demonstrated that near-misses operate in a qualitatively similar way to winning outcomes and enhance activity within frontostriatal circuitry and midbrain reward-related areas [34, 42, 43]. Such data intimate that near-misses promote a positive reward signal encoded by dopaminergic circuits. Dopamine neurons in the midbrain will fire in response to a primary appetitive stimulus, but if this stimulus is preceded with a cue that predicts its appearance, then these neurons will instead respond to this conditioned stimulus (see [44] for discussion). Aberrant dopaminergic signaling is a key component of drug addiction and has been suggested to drive the maladaptive attributions of salience to drug-paired cues that facilitate addiction [45]. Near-misses may be such an associative stimulus due to their structural proximity to a win; thus these sorts of trials may be able to evoke the representation of a win even in the absence of any reward. Although a definitive role for dopamine is currently unclear, there is general evidence that dopamine dysfunction may contribute towards problem gambling [46]. For instance, administration of the psychostimulant amphetamine, which potentiates the actions of dopamine, has been shown to increase motivation to gamble in problem gamblers [47]. Also, polymorphisms of both the dopamine D_2 and D_4 receptors have been associated with

increased prevalence of GD [48–52]. Lastly, a key role for dopamine in the pathology of behavioural addictions has been demonstrated by the iatrogenic GD that occurs in a small but significant subset of patients with Parkinson's disease (PD) [53] which arises *de novo* typically following adjunctive therapy with D_2-like agonists and generally abates following the cessation of these treatments [54].

The rSMT was designed specifically to function as an analogue of a simple slot machine. During the rSMT animals respond to a series of three flashing aperture lights, similar to the three wheels of a slot machine, and nose-poke responses in each hole cause the light to set to on or off. A win is signaled by all three lights setting to on, whereas any other light pattern indicates a loss. At the end of a trial, the animal chooses between the 'collect' lever, which delivers ten sugar pellets on winning trials, but a 10-s time-out penalty on losing trials, and the 'roll' lever which allows the animal to begin a new trial immediately. Similar to human gamblers, rats appear to exhibit a near-miss-like effect, responding on the collect lever significantly more when two out of three lights are illuminated. These sorts of trials therefore seem able to generate the expectation of reward, even after extensive training.

Reward expectancy on the rSMT is critically modulated by the dopamine D_2-like receptor family. Systemic administration of the D_2-like agonist quinpirole augments animals' expectations of reward, producing a robust increase in erroneous attempts to collect reward on nonwinning trials [33]. The D_2-like family contains D_2, D_3 and D_4 receptors, and of these the D_4 receptor appears to play the most crucial role in mediating performance on the rSMT. Systemic administration of a highly selective D_4 receptor agonist impairs performance in a similar manner to quinpirole, whereas a D_4 receptor antagonist decreased erroneous collect responses [55]. Thus, a D_4 agonist impairs, whereas an antagonist improves, animals' ability to differentiate winning from nonwinning outcomes on a simple slot machine, ostensibly through modulating animals' responsivity to reward-salient information. Unlike other members of the D_2-like family, D_4 receptors are located predominantly in prefrontal cortical areas engaged with higher-order cognitive processes and as such represent an intriguing target for modulating gambling-related behaviour [56]. Such a supposition has been bolstered by recent findings demonstrating that targeting prefrontal regions relatively rich in D_4 receptors such as the anterior cingulate cortex (ACC) and insular cortex also alters performance on the rSMT [57, 58].

The rSMT has highlighted a potential role for D_4 receptors in controlling salience attribution to reward-related stimuli and indicates that D_4 receptor antagonists might be useful pharmacotherapies for GD. However, such studies were conducted in healthy animals and do not address whether the rSMT can be used to model problematic engagement with gambling. One issue in developing an animal model of GD is that, like other addictive disorders, it is broadly idiopathic. However, iatrogenic gambling has been predominantly described in human patients following dopamine replacement therapy [53]. This particularly compulsive form of GD, along with other impulse control disorders (ICDs), is most often observed in patients with Parkinson's disease (PD), but has also been reported in patients with restless leg syndrome, fibromyalgia and prolactinoma following therapeutic administration of D_2-like agonists [59–61]. Thus these ICDs appear to arise directly as a result of the dopaminergic

drugs themselves, as opposed to a consequence of the neurobiological sequelae associated with PD. Therefore, recent investigations have attempted to model this particularly compulsive form of gambling using subcutaneously implanted mini-pumps to chronically deliver the $D_{2/3}$ agonist ropinirole to animals trained on the rSMT.

Chronic administration of ropinirole produced a robust increase in the number of trials animals completed and a reduction in the degree to which reward-related stimuli altered animals' ongoing behaviour [62, 63]. On their face, these behavioural changes resemble the increased desire to gamble observed in iatrogenic GD. These behavioural effects were also concomitant with a dramatic and prolonged increase in the inactive (phosphorylated) form of GSK3β in the dorsal striatum and an increase in the active (phosphorylated) form of CREB in the nucleus accumbens (NAc) [62]. CREB and GSK3β have been implicated in a broad range of functions including modulating learning and memory [64–66]. Both are activated by dopamine and contribute to subjective responsivity to drugs of abuse such as cocaine [65, 67–70]. However, any role for either protein in controlling gambling-related decision-making has, to our knowledge, not been investigated. Targeting one or both of these proteins could represent a novel treatment target for iatrogenic GD. Interestingly, preliminary data suggests that administering the β-adrenoreceptor blocker propranolol, which inhibits the phosphorylation of CREB in the NAC [71], ameliorates the compulsive-like task engagement observed following ropinirole, whereas dietary administration of lithium chloride, a potent GSK3β inhibitor [72], had no effect on task performance [63]. Thus, there is preliminary evidence that propranolol may be an effective therapeutic for iatrogenic gambling, putatively as a result of attenuating pCREB in the NAc.

In addition to the pharmacological data highlighting a role for dopamine in controlling slot machine engagement, recent data has suggested that animals that display increased 'optimism', in that they appear to interpret an ambiguous tone as more closely resembling a positive one, display impaired performance on the rSMT [73]. Such data may indicate that increased endorsement of other gambling-related cognitive biases may also confer susceptibility to increased reward expectancy and hint at a potential role for animal models in investigating the relationship between differing cognitive biases that may operate synergistically to confer vulnerability towards GD.

In summary, the rSMT is a reasonable facsimile of a simple slot machine. The task has repeatedly demonstrated that animals, like humans, are susceptible to win-related stimuli presented within a compound array, the so-called near-miss effect. Moreover, data from the rSMT suggests that D_4 receptors may be critically involved in mediating these attributions of salience to reward-related stimuli [55, 57, 58] and that augmented reward expectancy in response to near-miss-like trials may be indicative of other putatively pro-addictive constructs, such as optimism [73]. Additionally, chronic administration of D_2-like agonists appears to promote a compulsive-like endophenotype on the rSMT, indicating this task may provide a model for investigating problematic engagement with gambling, and inhibition of pCREB within the NAC may be an efficacious starting point for treatments targeting iatrogenic gambling [62, 63].

6.3 Impulsivity

Impulsivity, loosely defined as acting or making decisions without appropriate forethought, can in some cases be an adaptive trait. However, in excess, impulsivity inevitably results in deleterious consequences and is associated with a wide range of neuropsychiatric disorders, including the manifestation of both substance and behavioural addictions [74–77]. Impulsivity is a non-unitary construct that one recent model has proposed constitutes a two-factor process: an inhibitory process and an approach impulse process [78]. The inhibitory process, or response impulsivity, tends to be measured by motor disinhibition or impulsive action [79]. The approach process includes increased reward sensitivity and is typically parametrised as impulsive choice. Increases in both processes may confer vulnerability towards GD [79]. Operant behavioural tasks measuring impulsivity have tended to be classified into two similar areas: those that measure motor impulsivity and impulsive decision-making. The five-choice serial-reaction time task (5CSRTT) is perhaps the most widely used paradigm that contains a measure of impulsive action, or motor disinhibition, whereas delay discounting tasks have principally been used to measure impulsive decision-making (see [80] for discussion).

The 5CSRTT was designed as an analogue of the continuous performance time task (CPT), commonly used in human subjects, and the 5CSRTT has even been back-translated in human subjects, further confirming its validity [81, 82]. The CPT requires participants to scan a five-digit sequence and respond to a target sequence. Impulsive responses occur when a participant responds prematurely to a sequence that appears similar to the target. Similarly, the 5CSRTT requires animals to scan a five-hole array in order to accurately detect a brief light presentation (typically 0.5 s) in one of the apertures. The animal must make a 'nose-poke' response in the hole that was illuminated in order to gain food reward, thereby providing a measure of animals' visuospatial attention. Responses made prematurely, before the stimulus light is illuminated, generate an index of motor impulsivity [83]. The 5CSRTT has been widely adopted, and a significant body of work exists delineating pharmacological and neurobiological regulation of the task (see [83] for review). Amphetamine has reliably been shown to increase premature responding, an effect which appears principally mediated by dopamine [84]. However, amphetamine also affects other monoamines such as serotonin (5-HT) and noradrenaline [85], neurotransmitters that also modulate impulsive responding on the 5CSRTT (see [86] for review). Corticostriatal circuits appear to mediate these prepotent motor responses, as lesions to the infralimbic (IL) region of the mPFC, ACC or OFC increase premature responding [87, 88]. Similarly, lesions of the NAc also increase premature responding, but only on trials immediately following an incorrect response [89].

Although the 5CSRTT is arguably the most widely adopted task that includes a metric of impulsive responding, two other tasks that measure distinct aspects of impulsive responding are worth briefly mentioning, namely, the go-no-go and stop-signal tasks. The go-no-go assay measures action restraint, whereas the stop-signal task requires animals to stop a response that has already been initiated, or action cancellation. Both go-no-go and stop-signal tasks generally require animals to

perform a specific action, e.g. lever press in response to a 'go' cue, but inhibit this action in response to a no-go, or stop cue. During go-no-go paradigms, the go and no-go cues are never presented within the same trial, whereas in the stop-signal task, the stop signal is presented after some delay following the go signal. Thus, go-no-go requires animals to inhibit a prepotent response—in a similar manner to the 5CSRTT—whereas stop-signal task requires animals to withhold from making a response that has already been initiated. Although all of these tasks measure action restraint and appear superficially similar, there are key differences in both the pharmacological and anatomical underpinnings of these tasks. Broadly, neither task appears to be critically mediated by dopaminergic function [90]. Serotonin depletion impairs action restraint [91], whereas noradrenaline appears to be more involved in action cancellation [92]. However, both action restraint and action cancellation appear to be subserved by the OFC as well as striatal regions ([93, 94], but see [95]). A full discussion of these differences is beyond the scope of this chapter (see [86] for discussion, [96]). Rather, both tasks are mentioned here to highlight that there is considerable heterogeneity in the neurobiology underpinning a construct such as impulsivity, even within subdomains, and that differing neurotransmitter systems are recruited dependent on when the action inhibition signal is presented. Consequently, clarity regarding the cognitive process being tested must be considered when discussing findings from any behavioural test pertaining to measuring multifaceted constructs such as impulsivity.

Delay discounting is arguably the most widely used measure used to assess non-planning or impulsive decision-making. Impulsive choice on such tasks is measured by preference for smaller, immediately available rewards over larger delayed ones. The size of the reward and/or the length of the delays can be varied in order to generate a hyperbolic discounting curve. Steeper discounting curves, i.e. increased preference for smaller-sooner rewards, have been repeatedly shown in subjects with GD [18, 20, 97]. Animal models of delay discounting, like their human counterparts, require subjects to choose between either a small reward delivered immediately or a larger reward delivered after some delay [98]. Although multiple iterations of delay discounting paradigms have been developed for use in laboratory animals, perhaps the most widely used methodology is that based on Evenden and Ryan's original model [99]. In this task, animals choose between a small reward (typically one sugar pellet) delivered immediately and a large reward (typically four pellets) that is delivered after a delay. The delay increases in a stepwise fashion across blocks of trials, for instance, from 0, 10, 20 and 40–60 s. All trials are of an equivalent length, such that selection of the larger reward always results in more reward throughout a session. In a similar manner to premature responses on the 5CSRTT, delay discounting tasks are sensitive to pharmacological agents that potentiate the actions of dopamine. However, in contrast to the pro-impulsive effects on the 5CSRTT, administration of amphetamine, cocaine or a dopamine reuptake inhibitor increases choice of the large delayed reward, i.e. decrease impulsive choice [100–102]. However, it should be noted that amphetamine has also been reported to increase choice of the smaller immediate reward during delay discounting (see [80, 103] for discussion of methodological issues that may explain these seemingly

incongruous results). There are also some differences in regard to the neural loci that mediate impulsive choice and impulsive action. In contrast to impulsive responding on the 5CSRTT, ACC lesions do not increase impulsive decision-making during delay discounting [104]. However, the OFC does appear integral to optimal decision-making, in that excitotoxic lesions and inactivations have been shown to both increase and decrease choice of the large reward [105], dependent on task demands and baseline behaviour (see [106, 107] for discussion). Consistent with reports on the 5CSRTT, lesions to the NAc and ventral hippocampus both increase impulsive responding [89, 104, 108, 109].

Impulsivity is broadly considered to enhance vulnerability towards the development of both substance and behavioural addictions [75, 76]. A potentially related construct that has received relatively little attention, at least in regard to its potential role in GD, is compulsivity. The relationship between impulsivity and compulsivity is complex. Traditionally, these multifaceted constructs have been viewed as diametrically opposed, with individuals exhibiting a preponderance of one at the expense of the other, yet more contemporary theories now suggest that the relationship between the two is dynamic and can shift over time (see [110] for discussion). Whether compulsivity definitively constitutes a vulnerability towards GD is unclear. Certainly, the archetypal pathology of aberrant compulsivity, obsessive-compulsive disorder (OCD), is rarely co-morbid with GD, which would argue against such a conclusion [111]. However, gamblers do score higher on self-report measures of compulsivity [112], and the presence of OCD-like symptoms is well correlated with gambling severity [113]. Moreover, many of the cognitive distortions such as an adherence to 'lucky' rituals, which have been suggested as central to the development of GD [13, 14], could be considered compulsive in nature.

Selective serotonin reuptake inhibitors (SSRIs) are the primary pharmacological treatment for OCD and have reliably been shown to be effective at alleviating compulsive behaviours (see [114] for review). Consequently, animal work investigating compulsive-like behaviours has focused on the serotonergic system. The signal attenuation model consists of four stages: firstly, a compound stimulus is established as signal of food delivery, secondly, rats trained to lever press for food that is delivered concomitant with the compound stimulus, thirdly, signal attenuation, during which the ability of the cue to predict reward is attenuated by extinguishing the contingency between the two and, lastly, the test phase, during which rats lever press for the presentation of the stimulus alone [115]. An increase in responding on the lever during this test phase is hypothesised to reflect a failure in response feedback analogous to the inability of patients to cease responding once an action has been successfully completed [116]. Systemic administration of selective serotonin reuptake inhibitors or D_1 receptor antagonists alleviates compulsive-like responding on the lever [116, 117].

Further evidence of a potential role for dopamine in mediating compulsive-like behavioural responding comes from a relatively recent study using the operant observing response task. This paradigm presents animals with two levers, one an active lever that delivers food reward and the other inactive. There is also a third lever that, when pressed, signals which of the other two levers is active by

illuminating the light above the active lever [118]. In contrast to the signal attenuation model which intimated that D_1, but not D_2 receptors, may underlie compulsive behaviours, in the operant observing response task, chronic administration of the D_2-like agonist quinpirole significantly increased the number of responses on the 'observing' lever both in order to obtain the cue and also when the cue was already illuminated, potentially indicative of compulsive-like checking [118]. Interestingly, this increase in compulsive-like behaviour following chronic treatment with quinpirole may be related to the invigorated task performance on the rSMT following chronic ropinirole we reported in Sect. 6.2, in that the latter appears to reflect increased task 'focus'; animals on the rSMT were not quicker to make any particular response; therefore the increase in trials completed must have resulted from a decrease in other non-task-related activities, such as grooming or exploration. Furthermore, such an increase in task engagement superficially resembles the attentional narrowing observed in human gamblers, which is thought to reflect a compulsive style of play [119, 120].

In sum, impulsivity is a multifaceted construct that is influenced by multiple neurotransmitter systems. Broadly, dopamine, NE and 5-HT appear to be involved to some degree in action inhibition and impulsive choice, and such duplicity of neurotransmitter involvement may indicate some mechanistic redundancy in the control of these forms of impulsivity, whilst there may be a slightly more selective role for 5-HT and NE in action restraint and action cancellation, respectively. Interestingly, although all forms of impulsivity are sensitive to amphetamine, the direction of these effects varies depending on the form of impulsivity and the task demands, again further highlighting the complex nature of the construct and its measurement. Recent work has highlighted an important role for dopamine in mediating compulsivity, although the recruitment of receptor subtype appears to vary dependent on task parameters, and consequently, much remains to be done with regard to investigating the neurochemical basis of compulsive behaviours in animals. Moreover, chronic administration of dopaminergic agonists may be an effective way of modelling compulsive-like gambling engagement, and consequently these models may represent a potential method for screening novel pharmacotherapies for iatrogenic gambling.

6.4 Deficits in Decision-Making

Gambling broadly involves participants placing themselves at a probabilistic disadvantage for a potential windfall. In this regard, gambling could be considered irrational, insofar as people are generally aware that the odds of winning are stacked against them [121]. Thus the cognitive dysfunction exhibited by problem gamblers does not appear to be related to an inability to perceive or calculate the odds. Consequently, increased risky or dysfunctional decision-making could be considered as a hallmark for problem gambling. Although numerous other personality constructs such as those discussed in this chapter might contribute to the onset of problem (subclinical) gambling and GD, perturbations in cost-benefit decision-making are something of a

prerequisite. Gamblers' real-world decision-making deficits extend to the laboratory, with both recreational and pathological gamblers exhibiting deficits in comparison to healthy controls on tasks such as the Cambridge Gambling Task [17], Game of Dice Task [23] and the Iowa Gambling Task (IGT) [122]. These deficits are manifested when subjects are making decisions under both risk—choices between outcomes with explicit probabilities—and ambiguity, choices between outcomes with unknown probabilities, and cannot exclusively be accounted for by increased impulsivity or deficits in cognitive ability [122]. Consequently, decision-making deficits are, to a certain extent, dissociable from other behavioural facets of GD. Amongst these laboratory tasks, the IGT has been the most widely characterised, and consequently several rodent analogues have been developed (see [123] for discussion); in the interest of brevity, we will limit our discussion to the most widely adopted of these, the rodent gambling task (rGT) [124].

The IGT is generally considered as a test of 'real-world' decision-making and requires participants to select from four decks of cards, with the goal of accumulating points [125]. Two of the four decks are advantageous, in that they offer smaller immediate gains, but smaller penalties. In comparison the other two decks offer comparatively larger gains but also larger losses. The optimal strategy is to avoid the superficially alluring but ultimately disadvantageous decks and instead choose from the low-risk, low-reward decks. This strategy along with the relative contingencies for the decks is never made explicitly available to the participant, but healthy subjects learn the optimal strategy over time. Persistent choice of the disadvantageous decks has been linked to frontal lobe dysfunction and has been observed in both GD and drug addiction [22, 122, 125–128]. The rGT, consistent with the IGT, requires animals to choose between four options with established contingencies. Again, two options are disadvantageous, associated with larger gains (food reward) but more frequent and larger punishments (time-out periods), whereas the other two options are advantageous—associated with smaller gains but smaller and less frequent punishments. Animals have 30 min to maximise their 'earnings'; therefore these time-out periods reduce the opportunity to earn reward and were designed to approximate loss. Animals on the rGT show a similar behavioural profile to humans on the IGT, in that selection of the tempting high-risk, high-reward option declines as experience with the contingencies progresses and animals instead develop a clear preference for the smaller but safer rewards. The construct validity of the rGT has been tested by examining whether the neural loci underpinning task performance are comparable across species. Performance on the human IGT has consistently been shown to be critically dependent on brain regions that also putatively play a key role in the formation and maintenance of addictive disorders, namely, the prefrontal cortex and amygdala [125, 129–131]. Likewise, performance of the rGT is mediated by these same regions, lesions of the PFC and agranular insula impair choice behaviour, whilst inactivations of the orbitofrontal cortex and BLA or disconnection of these two areas severely retards learning of the optimal task strategy [132–135].

In contrast to other animal models of cost-benefit decision-making, dopamine does not appear to play a particularly prominent role; rather performance on the rGT is modulated by multiple pharmacological systems. Administration of selective DA

reuptake inhibitors, or D_1 or D_2-like agonists, does not alter choice behaviour [124, 136]. In contrast, administration of amphetamine and the 5-HT_{1A} receptor agonist 8-OH-DPAT both impair performance on the rGT [124]. Interestingly, the effect of amphetamine appears to arise as a result of additive effects on multiple monoamine neurotransmitter systems, as selective reuptake inhibitors for 5-HT, dopamine or norepinephrine produce only mild effects when administered in isolation, but any combination of two of the reuptake inhibitors impairs behaviour, potentially indicative of a redundancy in the neurochemical regulation of choice [137]. Furthermore, the effects of amphetamine on choice, unlike on motor impulsivity, cannot be blocked by either a D_1 or a D_2 receptor antagonist [138]. The finding that dopamine does not appear to play a particularly prominent role in the rGT is interesting given the relatively ubiquitous role ascribed for mesolimbic dopamine in cost-benefit decision-making. Much of this work has focused on animals' willingness to exert physical effort in order to obtain a larger reward—such as scaling a barrier or lever pressing. Broadly, blockade of dopamine receptors decreases animals' willingness to work for reward, whereas drugs that potentiate the actions of dopamine, such as amphetamine, increase the choice of the more effortful yet more lucrative option [139–142]. These data suggest that alterations in task demands may differentially recruit dopaminergic systems. Indeed, in contrast to the pronounced role dopamine plays in physical effort, it appears to play only a minor role if the effort required is cognitive [143]. Thus, the relative contributions of neurotransmitters, such as dopamine, to the choice process are critically dependent on task demands.

Probability discounting tasks (PDTs), in a similar manner to delay discounting paradigms, present animals with two levers, one of which delivers a small reward (e.g. one sugar pellet) with 100% likelihood, whilst the other lever yields a larger reward (e.g. four sugar pellets). In contrast to delay discounting, this reward is not devalued by a delay, but rather the likelihood of it being delivered is probabilistic and varies in a stepwise manner across the session. In the original iteration, the likelihood of the larger reward progressed downwards from 100%, 50%, 25% and 12.5–6.25%, although the probabilities can also be presented in ascending order [144]. There are some notable differences between delay and probability discounting, despite some similarities in the task structure. In delay discounting, both the large and small reward are always available, but the valence of the large reward is diminished by accompanying delay; thus the task measures the impulsive choice of immediate gratification over long-term benefits. In contrast, during probability discounting the large reward is not always delivered; thus the animal must decide whether to take the small safe reward or 'play the odds' and risk not receiving anything. During delay discounting, the larger delayed reward is always (at least objectively, if not subjectively) optimal, whereas the best strategy on probability discounting changes throughout the session, requiring animals to respond to shifting contingencies. Thus, preference for the uncertain outcome may not always be maladaptive, and the degree to which this maps on to the construct of impulsive decision-making is open to debate.

Unlike the anti-impulsivity effects amphetamine has on delay discounting, systemic administration of the psychostimulant increases choice of the larger

probabilistic reward [142], an effect contingent on amphetamine's ability to potentiate dopamine as indicated by its blockade by prior administration of either a D_1-like or a D_2-like antagonist. Similarly, administration of both D_1-like and D_2-like agonists increased choice of the uncertain option [145]. Similar to data from the delay discounting and 5CSRTT tasks, lesions to the NAc core increase maladaptive behaviour, as exemplified by increased choice of the smaller-certain option [144].

A risk discounting task (RDT) has also been developed that utilised electric shocks as punishments, i.e. the probability of reward was kept the same throughout the blocks, but the chances of a larger reward being accompanied by a footshock increased throughout the blocks (25%, 50%, 75–100%). There is a modest correlation between probability and risk discounting, suggesting some of the same cognitive processes may be implicated in both tasks [146]. In contrast to its effects on the PDT, amphetamine decreases choice of the larger, but potentially punishing option on the RDT, an effect blocked by a D_2-like antagonist. Likewise, a D_2-like agonist decreases risky choice, whereas drugs targeting D_1-like receptors have no effect [147]. Comparing the neurochemical regulation of choice behaviour across the rGT, PDT and RDT suggest that the neurobiology underlying risk-based decision-making may vary contingent on the presence or absence of explicit penalties, as well as the nature of those penalties, further complicating delineating a singular aetiology for human gambling.

One potentially interesting, and relatively underexplored avenue, is what governs decision-making in the absence of optimal choice. In the majority of operant paradigms, the probabilities are such that there is almost always an optimal strategy. Arguably a better measure of biased decision-making would be to examine choice behaviour when options are ultimately equivalent. In the rodent betting task (rBT), the 'bet size' in play is indicated by the illumination of one, two or three response apertures at the start of each trial [148]. The bet size varies between blocks of trials on a pseudorandom schedule. Once the animals have nose-poked at each illuminated aperture, two levers are extended into the chamber. These levers are permanently designated as either the 'safe' or 'uncertain' lever. Responses on the safe lever lead to guaranteed delivery of the bet size at stake (i.e. one, two or three sugar pellets), whereas the uncertain lever leads to either double the safe bet size or no reward with equal probability. Thus, exclusive choice of either option would lead to equivalent reward in the long term. Initial investigations with this task revealed that animals could broadly be split into two sub-groups—one that remained indifferent to the size of the wager (insensitive) or those that began to select the safe lever more as the bet size increased (sensitive).

In contrast to the rGT, choice behaviour on the rBT is acutely sensitive to manipulations of OFC, as inactivations of this region, but not the mPFC increased risky choice in wager-sensitive rats [149]. However, lesions to the basolateral amygdala did not affect performance, regardless of baseline choice patterns [150]. As such, simple preference for uncertain outcomes, as measured by an unbiased paradigm, can be dissociated from the adoption of an optimal choice strategy in which the risks of winning and losing must be integrated.

Systemic administration of amphetamine increased choice of the uncertain lever, but only in wager-sensitive animals, whereas the D_2-like antagonist eticlopride

decreased choice of the uncertain lever, but only in wager-insensitive rats. Thus animals' baseline choice behaviour critically mediated the response to dopaminergic ligands. Using micro-PET and autoradiography, a strong relationship was confirmed between increased wager sensitivity and lower levels of $D_{2/3}$ receptors in the striatum [148]. A decreased density of striatal dopamine receptors has been proposed as a canonical biomarker for drug addiction. These results may therefore suggest that mathematically nonnormative decision-making under uncertainty, which is associated with elevated risk for GD, may arise through similar neurobiology as traits which confer vulnerability to drug addiction [151, 152]. Moreover, these results highlight the potential value in exploring individual differences in animal models of decision-making, as differences in subjective choice at baseline can shape later response to pharmacological challenges. Further studies utilising this task have shown that chronic administration of ropinirole increases choice of the uncertain lever and such results not only highlight the critical role played by dopaminergic activity in mediating risk-based decision-making but arguably provide further evidence that chronic $D_{2/3}$ agonism may represent a putative model of problem gambling [153].

Ultimately, perturbations in cost-benefit decision-making are varied, and task demands such as response requirements, the valence/volatility of the outcome and consequences of loss/failure to win can all affect how animals engage with the task. Although broadly the majority of these tasks remain sensitive to dopaminergic and/or serotonergic manipulations, alterations in task design and individual differences can have profound effects on the neurobiology recruited.

6.5 Cue Reactivity

The ability of cues to facilitate ongoing addictive behaviours is a cornerstone of contemporary theories of addiction [45, 154–156]. However, the relevance of cues to GD is less clear. Certainly exposure to gambling-related cues can promote craving in gamblers [24, 25], and removing sound cues reduced both the enjoyment derived from and the desire to continue playing slot machines in problem gamblers [157]. Additionally, problem gamblers have been reported to display attentional bias towards gambling-related stimuli in comparison to controls (see [158] for review), and an increased attentional bias towards salient cues has been suggested to contribute to the transition from recreational to problematic gambling [26]. These data ultimately suggest that cues are an integral part of the gambling milieu, yet the exact role cues play in the formation or maintenance of GD and the contextual specificity of gambling cues remain to be determined (see [159] for discussion).

Relatively few animal tasks have specifically addressed the role of cues on gambling-related decision-making, with the notable exception of a modified version of the rGT, wherein reward delivery resulting from choice of the larger, but riskier, options is associated with more salient and complex audiovisual cues [160]. Interestingly, the presence of cues promotes a more disadvantageous choice profile, with more rats exhibiting a risk-preferring profile at baseline, providing the first

evidence in non-human animals that reward-paired audiovisual cues can promote risky decision-making [160]. Moreover, the presence of cues on this modified rGT recruited the dopaminergic system to a greater degree than the uncued version. As mentioned in Sect. 6.4, the rGT does not appear to be greatly influenced by dopaminergic agents, yet choice on the cued rGT appears uniquely sensitive to the administration of compounds specific for the D_3 receptor; a highly selective D_3 agonist increased, whereas a selective antagonist decreased risky choice. These findings are in direct contrast to the lack of effects D_3 ligands produce on the 'standard' rGT [161] and provide novel evidence that D_3 receptors may play a role in controlling responsivity to gambling-related cues. In support of such a supposition, D_3 receptors have previously been demonstrated to mediate cue-induced seeking of addictive drugs and consequently have been suggested to represent a potential pharmacological target for the treatment of drug addiction [162–165]. Given the theory that the phenomenological processes underlying both behavioural and substance addictions may be similar, D_3 receptors may represent something of a common target for controlling certain aspects of behavioural dysfunction.

It is worth noting that in the cued rGT, the cues are concurrent with reward—and absent following a loss. In contrast, cues during the rSMT signal the current status of the apertures and function as predictors of reward (reward-predictive), as opposed to being delivered subsequent to the trial outcome (reward-concurrent). Thus, whilst both tasks contain overt cues, the cues signal very different information and may therefore impact cognition via distinct mechanisms. Certainly, these different cue-mediated behavioural effects appear pharmacologically distinct, as selective D_4, but not D_3, ligands alter performance on the rSMT [55], whereas targeting D_3, but not D_4, receptors modulates behaviour on the cued rGT [160].

In contrast to the relative dearth of empirical investigations examining the role of cues on cost-benefit decision-making, a comparatively larger body of evidence exists using simple behavioural tasks that have been used to delineate the neurobiological underpinnings of cue-guided responding. Similar to both the cued rGT and the rSMT, the role of dopamine in controlling cue reactivity has been the predominant focus of these investigations. Dopaminergic signaling particularly through the D_2-like class of receptors has been generally associated with attributing salience to reward associated stimuli [166]. Indeed, this process plays an important role in some theories of addiction (see [45] for discussion). Relatively simple behavioural paradigms such as autoshaping, as well as a Pavlovian-to-instrumental transfer (PIT) and conditioned reinforcement (CRf), have been used most commonly. Ostensibly all these paradigms measure how reward-paired cues can influence action, but differ slightly in regard to brain areas and neurochemical regulation. These tasks could be considered hierarchical in that the property of the cues increases in behavioural significance, from attracting attention (autoshaping), to influencing ongoing behaviour (PIT) and finally to becoming the goal itself (CRf).

During autoshaping, a classically conditioned stimulus (CS) reliably predicts delivery of an unconditioned stimulus (US), for instance, presentation of a lever and accompanying light (CS+) for 5 s before a food pellet (US) is delivered. Over repeated CS-US pairings, some animals begin to approach and interact with the CS,

even though the US is not contingent on any such response. Typically animals vary in the extent to which they respond to the CS and can be separated into those who approach the CS, i.e. 'sign trackers' (ST), and those who orient towards the delivery location of the US, i.e. 'goal trackers' (GT) [167]. The incentive salience assigned to the CS by sign trackers has been linked with increased dopamine release within the NAc [168], and both acquisition and expression of sign tracking can be disrupted by administration of non-selective dopamine antagonists [169]. Whilst sign tracking could be taken as evidence that reward-paired cues are salient and attractive, it does not necessarily imply that they can influence goal-directed action.

PIT measures the degree to which a CS that has previously been classically conditioned with reward can invigorate instrumental responding that has, in separate training sessions, also resulted in reward. PIT begins in a similar manner to autoshaping, in that a CS, e.g. a tone, predicts delivery of a US (food). Subsequently animals are shaped to make an operant response for reward such as lever press. Lastly, during a test session, usually done during extinction (i.e. reward is not delivered), the CS is presented with the supposition that the presentation of the CS will augment animals' operant responding on the lever. The CS is presented intermittently and non-contingently; thus the animals' actions do not affect the presentation of the CS, yet the CS can bias the animal towards actions previously associated with reward delivery. PIT is sensitive to modulation of dopaminergic circuits (see [170] for discussion) and can be disrupted by systemic administration of non-selective dopamine antagonists [171].

In a somewhat similar manner to PIT, CRf begins with classically conditioning a CS to delivery of a US. Yet in contrast to PIT, the subsequent test session determines the degree to which an animal is prepared to perform a novel response, such as lever pressing, that is reinforced solely by the CS. Thus, in contrast to PIT, the presentation of a CS during CRf is entirely contingent on the animals' behaviour. CRf appears to be primarily influenced by dopaminergic activity within the NAc, as infusion of amphetamine into this area potentiates animals' responding for the CS, an effect that is remediated by prior blockade of D_1 or D_2 receptors [172]. Similarly, infusion of non-selective D_1-like or D_2-like agonists into the NAc potentiated responding for the CS, an effect that was mimicked by a systemically administered D_2-like agonist, but not a D_1 receptor agonist [172, 173].

In broad terms, therefore, performance on all three of these tasks has been shown to be sensitive to ligands with selectivity at D_2-like receptors [174–176] and more specifically manipulations of dopaminergic activity within the NAc [177–179]. The NAc receives extensive inputs from cortical and limbic regions and has been suggested to be critically involved in response selection, yet the upstream inputs that might be important for driving behaviour during the performance (rather than the acquisition) of tasks such as autoshaping or CRf remain elusive [180]. Interestingly, recent work from our group showed that a highly selective D_4 agonist had no effect on either CRf or autoshaping [181]. Additionally, mixed results have been observed with partially selective D_3 agonists, and more selective D_3 antagonists are without effect on simple behavioural tasks [176, 182], intimating that D_3 receptors cannot exclusively account for responsivity to CS+. Interestingly,

increased cue-driven behaviour on CRf and autoshaping, a putative biomarker for addiction vulnerability, is associated with lower levels of impulsivity [183]. Additionally, we have preliminary evidence that suggests animals' instrumental motivation for cues on a CRf paradigm does not correlate with performance on either the regular or cued version of the rGT (Tremblay, Ferland, Hounjet and Winstanley unpublished observations). Thus, increased cue reactivity, at least as assessed by CRf and autoshaping, is not associated with increases in either impulsivity or perturbations in cost-benefit decision-making, canonical measures of dysfunction in addictive disorders. Clearly, in this regard we are comparing between relatively simple behavioural tasks and much more complex ones. Decision-making on more intricate tasks likely promotes a higher cognitive load; consequently, behaviour is unlikely to be exclusively influenced by stimulus-response relationships. In contrast tasks such as autoshaping, PIT and CRf, although useful insofar as they have reliably intimated that the D_2-like receptor is critically involved in mediating approach behaviour, may be somewhat limited in regard to exploring more complex disorders such as addiction, where the cognitive processes involved are likely complex and multifactorial. The likelihood of approach, or motivation to obtain a CS+, may therefore be a weak facsimile of the more complex role cues play in behavioural or substance addictions.

In sum, unlike the other sections of this chapter that have generally highlighted a complex interaction of the monoamine neurotransmitters in controlling behaviour, cue reactivity appears to be principally mediated by dopamine. This is not all together surprising given the canonical role ascribed [44] to dopamine in signaling the appetitive value of environmental stimuli. However, the role for dopamine in mediating animals' responsivity to cues is nuanced and dependent upon the complexity of the task and the contextual quality of the cues.

6.6 Conclusions

We have argued here that excessive cognitive distortions, impulsivity, compulsivity cue reactivity and impaired cost-benefit decision-making may confer vulnerability towards GD. The criteria discussed here may offer an opportunity to 'deconstruct' some facets of behavioural dysfunction observed in problem gambling. Indeed, it is unlikely, given the heterogeneity of gambling that any human gambler would exhibit perturbations in all of these symptom domains. Thus, a more comprehensive understanding of subtypes within gamblers may be useful in delineating a conceptual framework to explore the underlying neurobiology using animal models and consequently treatment development. However, animal models may also be useful for exploring the relationship between these constructs, given recent data indicating that increased impulsivity is associated with a greater endorsement of gambling-related cognitions [184].

These putative risk factors appear to have overlapping but discrete neurobiological underpinnings. Broadly speaking, a common role can be attributed to the monoamine transmitters dopamine, 5-HT and noradrenaline as well as frontostriatal brain

regions. A role for both 5-HT and dopamine in mediating aspects of impulsivity and impaired cost-benefit decision-making is relatively well established. Importantly, the data here offer at least two relatively novel potential lines of enquiry. First, the potential role for D_3 and D_4 receptors in mediating differing behavioural responses to reward associated stimuli has yet to be fully explored. Data from the rSMT indicate that D_4 receptors might control attributions of salience to reward-predictive stimuli, whereas D_3 receptors appear to mediate risky choice in response to reward-concurrent cues. The majority of studies that target D_2-like receptors often attribute their findings to the D_2 receptor itself, potentially due to its relative abundance within the D_2 family [185] and its localisation within reward-related neural structures such as the dorsal striatum and NAc [186]. However, the results highlighted here may be indicative of an increased role for D_3 and D_4 in the more complex cognitions associated with GD.

A common theme throughout this chapter has been that tasks pertaining to measure the same construct can recruit differing neurobiological systems. This variability is by no means a weakness of animal models. In fact, both the inter- and intra-task variability may be invaluable at gaining a more comprehensive understanding of the aetiology underlying behavioural disorders. Moreover, the individual differences within animals could also be extremely beneficial in identifying what forms of interventions may best be used to combat differing behavioural perturbations. These differences, however, do signify considerable variability within constructs such as impulsivity, such that care should be taken not to extrapolate too widely from one paradigm to another. The variability both within and between some of these tasks does lead to questions about reliability. As there is no currently approved pharmacological treatment available for GD, pharmacological isomorphism is not a good measure of assessing these tasks' validity. However, one of the cornerstones of a valid operant measure is reliability. As all of these tasks have been used repeatedly, in most cases by different researchers, the retest reliability of the core behavioural observations discussed herein appears high. However, there are intractable issues with animal models that potentially limit their efficacy, mainly in regard to how both rewards and losses are represented (see [32] for full discussion of these potential limitations).

Ultimately, despite limitations, animal models with high translational validity allow a degree of control and breadth of manipulations that allow inferences about the causality of clinical disorders. This control and range may be invaluable in elucidating a more comprehensive understanding of diseases such as GD where the aetiology is complex and multifactorial.

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