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Translating concepts of risk and loss in rodent models of gambling and the limitations for clinical applications

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Abstract

Gambling involves placing something of value at risk in exchange for the opportunity to potentially gain something of greater value in return. A variety of gambling paradigms have been designed to study the maladaptive decision-making that underlies problematic gambling. Central to these gambling models are the definitions of “risk” and “loss”, especially when translating the results from rodent studies to clinical applications. Risk and loss are not mutually exclusive but rather share some overlap. With careful interpretation and consideration of the limitations of these behavioral paradigms, results from rodent models may provide insights into the neurobiology of risky decision-making that leads to problematic gambling in humans.

Keywords

gambling; risk; Loss; Rodent Models; decision-making

Introduction: Risk and loss in human gambling

Gambling involves placing something of value at risk in exchange for the opportunity to potentially gain something of greater value in return. While the occasional gamble can be serendipitous, excessive gambling typically results in substantial financial losses [1,2]. In fact, Gambling Disorder (GD) is characterized by persistent maladaptive decision-making that leads to significant distress and impairment [3,4]. The prevalence of GD in United States adults is estimated to range anywhere from 0.4 to 4.2% [2,3,5]. Given the high rates of comorbidity with psychiatric and substance-use disorders, and lack of effective

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pharmacological therapies for disordered gambling, both human and rodent studies are necessary to better understand the neurobiology of risky decision-making and etiology of GD.

Disordered gambling often consists of suboptimal and maladaptive decision-making, which is largely influenced by the uncertain probability and magnitude of potential reward outcomes. Within recent years, development of novel behavioral tasks have allowed scientists to investigate the effects of uncertainty and risk on decision making in animals. These tasks include the rodent gambling task (rGT), the probabilistic delivery or discounting task (PDT), the delay-discounting task (DDT) and the risky decision-making task (RDT). Yet, a key discrepancy between these gambling-like paradigms and human gambling must be noted --the manner by which each task attempts to model “loss” [6,7]. These differences, although subtle, may reflect nuanced psychological and neurobiological aspects of gambling and risk-taking behavior. Thus, it is imperative that representations of risk and loss are taken into careful consideration when interpreting the results and assessing the clinical implications of these findings.

Teasing apart definitions of risk and loss

In both humans and rodent models, “risk” can be defined by uncertain outcomes that vary in magnitude and/or probability. Risk, as the perceived value or valence of future outcomes, may be positive, negative, or neutral [6]. The probabilities of these outcomes can also be uncertain, adding further complexity into decision-making, as one must consider the probability of reward (i.e. odds of a win), probability of loss (e.g. time, money), or probability of adverse consequences (e.g. physical punishment) [8–12]. In contrast, “loss” is captured by the decrement and reduction of valuable and often limited resources. In the context of gambling disorder, loss primarily refers to financial/monetary loss, but can also take the form of a loss of time and energy, social relationships, employment, etc. In extreme cases, repeated gambling behavior can come at a cost to one’s health due to increases in depression, anxiety, or general health outcomes, as gambling disorder is associated with greater rates of suicide [13–16].

Risk and loss are not mutually exclusive

Risk can be thought of as a form of uncertainty [17], where the particular outcome of a given choice is, at best, known to exist within a defined range of possible outcomes and, at worst, fully unknown [6,18]. The value of possible outcomes for a risky choice can range from positive to negative, where positive outcomes are greater than what was wagered and negative outcomes involve some detriment or loss from the initial starting point (Figure 1). When the possible outcomes range across several positive outcomes (uncertainty in reward magnitude) or from positive to zero (uncertainty in the probability of reward), then risk can be thought of as existing in the absence of any possible loss. In contrast, when the range of possible outcomes spans within the negative range (positive to negative; zero to negative; or magnitudes of negative) then a choice truly encompasses the possibility of loss. This suggests that risk and loss are not mutually exclusive but that, within a certain range, possess some overlap.

Risk in the absence of loss only becomes truly problematic in situations where the individual is bound by limited resources (e.g. food, time). Within such parameters, risk naturally varies as a function of the flexibility of resources. For example, for someone with an almost unlimited amount of financial wealth, or an animal with ad-libitum access to food, the risk of not winning becomes negligible. However, degrees of food restriction in animal models can potentiate the value of risk despite leaving reward uncertainty untouched [19], yet for good reason can never truly produce loss in the way that financial debt can do so in extreme cases of human gambling. In many cases, loss in gambling involves both short-term (e.g. insufficient funds to participate in unnecessary activities such as vacations) and long-term (e.g. increasing debt and the inability to pay one's rent or credit card bills) consequences. However, in animal models, loss is most often captured on the short- (e.g. absence of reward during a particular trial) to medium-term (e.g. longer time delays to gain reward within a given session), thereby highlighting one of the translational limitations of rodent gambling models.

Uncertainty amplifies risk and loss

The valence ascribed to these types of risk can be influenced by environmental factors, past choice history, and physiological state. Value assessment allows an individual to weigh the costs and benefits of a choice and direct behavior [10]. Additionally, there are substantial individual differences in how risk is processed and perceived. Risk can be processed objectively, as the variance in possible choice outcomes, or processed subjectively, as the value attributed by the individual to that variance in outcomes [20]. Hence, risk typically degrades the subjective value of a choice option in individuals who are risk-averse, whereas risk enhances subjective value in risk-seeking individuals [21,22].

Although decision biases may predispose individuals to gambling disorder, many have argued that the uncertainty of reward, the risk, is a key factor in making gambling both highly engaging and potentially addictive [23]. Furthermore, this reward uncertainty has been shown to enhance attentional bias and attraction towards gambling-related cues in both rodents [24–26] and individuals with gambling addiction [27]. Clinical studies have reported that participants exposed to cues previously associated with large risky wins were more likely to choose the riskier option and negated their natural tendency for risk-avoidance [28]. This “choice signaling” has also been shown to increase preference for a risky choice in pigeons and macaques [29,30]. Therefore, investigating how risk is processed and directs decision-making has important implications for individualized approaches to prevention and treatment of gambling disorder and other addiction-like behaviors.

Measuring risk and loss in animal models of gambling

Rodent models of risk

Unlike drug-addiction models, models of gambling disorder in animals have traditionally focused less on the compulsive nature of the behavior, focusing instead on deficits in decision-making (i.e. irrational choices) which are thought to underlie disordered gambling. The most common of these behavioral paradigms is the rodent gambling task (rGT), an analog to the human-based Iowa Gambling Task (IGT) [31–33]. In this task, some rats

display a decision bias, preferentially and persistently choosing the high-reward/high-risk options, a characteristic pattern of behavior of individuals with gambling disorder [11]. Most recently, studies examining decision bias suggest that decision-making on the rGT can be influenced by the presence of reward-paired cues [34] and penalty events designed to approximate losses [35].

While decision biases may predispose some individuals to gambling disorder, substantial evidence supports the idea that the presence of reward uncertainty makes gambling highly engaging and potentially addictive. To that end, Laskowski et al. trained animals for 6 weeks under either fixed or random ratio schedules for food reward, to examine whether prolonged exposure to a risky, gambling-like reward schedule could induce addiction-like symptoms in rats [23]. Their results suggest that tasks with random reinforcement schedules (i.e. risk of no reward or large reward at varying probabilities) largely failed to increase responding when reward was unavailable, and had no significant effect on reinstatement of reward-seeking, or persistence in the face of increasing punishment (i.e. reward devaluation by footshock pairing). However, they did note that during these tasks with uncertain reward reinforcement, rats did increase response rates, shorten pauses after rewards, and tended to show higher break points on a progressive ratio. These findings demonstrate that exposure to risk, in the form of uncertain reward delivery, enhanced motivation to engage in the task, but did not lead to the development of compulsive, addiction-like behaviors [23]. On the other hand, random ratios of reinforcement have been shown to increase risky decision-making, but only after extensive training on the rGT [36]. Thus, risk, as defined by uncertain reward outcomes, motivates gambling-like behavior but alone is insufficient to drive compulsive, addiction-like patterns of behavior seen in human gamblers.

Rodent models of loss

Alternatively, risk can be defined by adverse consequences associated with a reward outcome. This form of risk is perhaps best modeled by the risky decision-making task (RDT), in which animals are given choices between small, safe rewards, and large rewards accompanied by an increasing risk of physical punishment (footshock) [37,38]. Recent studies report that decision-making under risk of footshock punishment is selectively modulated by dopamine signaling [39], predominantly through D2 receptors [40]. However, the complex role of dopamine in risky decision-making only further highlights the importance of adequately defining risk in animal models of gambling [12,41]. For example, chronic administration of D2/3 receptor agonist ropinirole during a rodent Betting Task (rBT) reportedly increased risky choice in two-thirds of the animals, regardless of individuals' baseline risk preference [42]. However, the identical drug treatment had no effect on risky choice during a cued and uncued rGT [43], nor during a rodent slot machine task (rSMT) [44].

Risk preference on the RDT is also associated with increased impulsive action, but not impulsive choice or habit formation [45]. RDT studies show that prior exposure to cocaine self-administration, but not sucrose, increased the proportion of risk-taking individuals, and greater risk-taking predicted greater cocaine intake during acquisition of self-administration [46]. In comparison, risk preference on the rGT has also been associated with increased

impulsive action [47] but not increased cocaine-taking [48]. Collectively, these studies have emphasized the impact of strong individual differences in choice/risk bias, with some animals displaying a risk-taking phenotype, while others are more risk-averse [21,32].

Similarly, increased risk-taking in the RDT predicted locomotor sensitivity to first-time nicotine exposure and resilience to nicotine-evoked anxiety [45]. Considering the high level of comorbidity between substance use disorders and gambling disorder (57.5%) [5,49,50], and that more than half of pathological gamblers (60.4%) report comorbid tobacco dependence, compared to only 16.8% of the general population [24,51], task such as the RDT may prove useful for highlighting some of the behavioral and neural commonalities between substance users and gamblers and may help identify a shared mechanism for either pathology.

Models that combine risk and loss

Since most rodent paradigms involve behavioral tasks in which risky choices are reinforced with a food reward that is immediately received and consumed, these models fail to replicate a key feature of gambling in humans: wagering and losing a bet. In other words, the valence of a loss of an already possessed reward is not the same as a failure to gain additional rewards [11,43]. Recently, novel paradigms have been developed to address these discrepancies. For example, in the rodent Betting Task (rBT), rats are given a choice between a certain outcome (that changes across trial blocks within a session) versus the chance to bet on a risky option that half the time gives double the reward, or no reward. This design attempts to measure “escalation of commitment”, such that as the stakes increase/losses escalate (50% chance of double the prize or nothing), the individual becomes more risk averse, even if the odds of success remain constant [52]. Previous studies have shown that as the amount of reward at stake increases, some rats irrationally shift their preference towards the guaranteed outcome, whereas other individuals remain indifferent to the change in wager size [42,44]. This shift away from the uncertain option as the bet size increases, or “wager-sensitive” phenotype, resembles behavior biases seen in human gamblers [52].

In addition to the influence of wager size, the “near-miss” phenomenon can also affect risk affinity and increase the addictiveness of gambling games such as slot-machines [41]. In human subjects, near-misses were subjectively described as “less pleasant” than full-misses, yet near-misses increased desire and motivation to play when the subject had direct control over arranging the gamble [53]. However, a recent study in humans failed to corroborate a causal relationship between the near-miss effect and gambling persistence [54]. The near-miss hypothesis was first espoused by Skinner [55], but studies investigating this effect in rodents have been sparse. Recently, a rodent slot machine task (rSMT) reported evidence of the near-miss effect in rats, such that “almost winning” was more similar to winning, despite the absence of reward reinforcement [41].

Another aspect of gambling games believed to encourage continued playing despite losses or adverse consequences are “losses disguised as wins” (LDWs), that is outcomes in which the money returned is less than that wagered. Despite the net loss to the player, both novice and experienced gamblers report that LDWs were rewarding and reinforcing-extending playtime and even influencing game selection, such that players prefer games with high positive

payback percentages [56,57]. However, the cognitive and neurobiological mechanisms attributing motivational properties to LDWs, and their contribution to gambling addiction, remains largely unknown.

Ferland et al. reported that while most LDWs shifted rats' choice towards the safe lever, a subgroup of animals persisted choosing the risky lever. Interestingly, inactivation of the basolateral amygdala (BLA) reproduced this persistent selection of the risky and suboptimal choice, suggesting this pattern of behavior may be facilitated by impaired or disrupted BLA functioning [58]. Other recent studies in rodents suggest that LDWs may encourage "loss-chasing" by increasing reward expectation and by increasing stay-biases for the risky choice [59]. Furthermore, in these tasks, LDW outcomes are typically accompanied by salient, reinforcing visual and auditory cues, which may further motivate continued playing [35,60–62].

Current limitations to measuring risk and loss

A considerable limitation in rodent models of gambling is the pervasiveness of loss in other aspects of life. In humans, loss can be applied to areas outside financial means, such as distress and impairment that spreads into the individual's personal life, social life, and professional career [4]. In contrast, a loss in the context of a rodent model of gambling is confined to the daily experimental session. A loss of sugar pellet rewards in a 30-minute choice session does not have long-lasting implications that affect the rat's or cagemate's living situation. As such, many of the forms of loss typically modeled in rodent studies can be seen as the loss of a resource or the addition of a punishment. In particular, punishments such as the administration of a brief footshock fail to mimic the long-lasting consequences that are normally incurred in gambling disorder. Recently, attempts have been made to examine the effect of delayed punishments as in the delayed punishment decision-making task (DPDT) [63], although the impacts are still only restricted to within a given session.

Another distinction between human gambling and rodent gambling is the concept of "loss of time." Whereas gambling in humans may begin as a recreational behavior which only draws a limited amount of attention and time away from other activities, as gambling disorder develops, gambling may rapidly become the sole activity of interest, and consume extensive amounts of time [64]. In contrast, rodent gambling tasks are usually of very limited duration, lasting typically between 30 minutes and 2 hours; unlike studies of drug addiction which have recently evolved to include extended access models lasting up to 6 h[65]. Crucially, however, in many rodent models of gambling, risky decision-making and gambling-like behavior are characterized by choices that result in loss of time, which here reduces the time the animal spends making risky choices and "gambling", rather than increasing and extending the animal's opportunity to gamble.

An additional limitation in relating rodent models of gambling to human gambling behavior is the discrepancy between a rat's concept of money or financial loss to that of a human. Since rats cannot be motivated by money, most gambling tasks using animal models utilize sucrose rewards to motivate and reinforce choice behavior. Thus, loss in rodent studies can be signaled by the absence of reward, or a reward plus an adverse consequence (i.e. physical

punishment, delayed reward, increased effort, etc.). This technique becomes problematic when translating findings into clinical applications since money is a secondary rather than primary reinforcer [66], and research suggests that these secondary reinforcers may engage different brain circuitry than biologically relevant stimuli such as food [67,68]. In rodent models of gambling, sucrose pellets serve as the only reward type and only vary in magnitude. As a result, rodents are “working” for one unexchangeable reward, while humans in real life gambling games are working for a reward that can be further leveraged to obtain more desirable rewards. In addition, one major challenge is that whereas money can be both amassed and lost in large quantities, food rewards in rodents can both produce satiation and interfere with motivation to “play” and, conversely, cannot be easily subtracted or withdrawn, but simply withheld.

Conclusion

Modeling gambling behavior and examining the factors that lead to the development of gambling disorder requires complex animal models of gambling behavior. This can only be achieved by clearly defining the concepts of risk and loss, and assessing their relative contributions to risky choice and an individual’s choice bias. Here, we highlight several recent tasks that have attempted to model various forms of risk and loss and pinpoint some of the limitations and challenges of modelling loss in animal models of gambling behavior. Although these are difficult challenges, the recent rise in the number of new tasks exploring gambling-like behavior is promising and offers insights into the etiology of risky decision-making and novel approaches to prevention, identification, and treatment of gambling disorder.

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Highlights:

- Defining risk and loss is important when translating rodent models of gambling
- Risk and loss are not mutually exclusive but may overlap within the range of outcomes
- Risk involves assessment of the values of all possible but uncertain outcomes
- Loss refers to the reduction or decrement of valuable and often limited resources
- Rodent models studying risk and loss have limitations to clinical gambling applications

Figure 1:

Risk can be defined as the range of all possible, but uncertain, outcomes from positive (most optimal) to negative (most suboptimal) in terms of both reward magnitude and probability. In contrast, loss constitutes a subcategory of risk that is a negative outcome in the form of punishment or loss in a particular limited resource. Appropriately simulating risk and loss is arguably one of the biggest challenges in accurately modelling gambling behavior.