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Challenges and Opportunities in Animal Models of Gambling-like Behavior

Cole Vonder Haar

Injury and Recovery Laboratory

Department of Psychology, West Virginia University, Morgantown, WV, USA

Department of Neuroscience, West Virginia University, Morgantown, WV, USA

Abstract

In the past several years, there has been an explosion of interest in animal models of risk-based decision-making, a fundamental process associated with gambling disorder. While early work focused on establishing various tasks for assaying decision-making, current studies are determining the (subtle and not-so-subtle) influence of cues in driving risky decisions to better understand problem gambling. In addition, these decision-making paradigms are now being used to investigate comorbid conditions such as substance dependence or brain injury and replicating observations from human patients. These animal models have now developed to a point where therapeutic interventions may be assessed for not just gambling disorder, but also a number of other conditions which engender risky decision-making.

Keywords

Decision-making; cues; environment; brain injury; addiction

Introduction

Although gambling is typically considered a human topic, decisions involving risk or uncertainty are a fundamental feature of behavior. One classic example of this is the case of foraging. Even if an animal has a source of food, that source may eventually become depleted, and so decisions must be made regarding exploration of their environments to obtain more. Although foraging may lead to risk of predation, evolutionary pressures likely favor decisions that involve some degree of risk-taking. Given that the neurobiology

Corresponding author: Cole Vonder Haar, Department of Psychology, West Virginia University, PO Box 6040, 53 Campus Drive, Morgantown, WV 26505, Tel: 1-304-293-1787, Fax: 1-304-293-6606, cole.vonderhaar@mail.wvu.edu.
Author's note: including "risky" or "risk" will generate toxicology and related papers, and the term "probabilistic" may pull in papers from a variety of disciplines.

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mediating such behavior likely overlaps between species, animal models represent an opportunity to gain a better understanding of the factors that contribute to human psychopathology involving decision-making under risk.

The current paper focuses on recent findings across the animal literature of risky decision-making, with special reference to models mimicking human gambling disorders. Although a relatively small subfield, the literature examining decision-making under risk has grown remarkably in recent years (Figure 1)¹. The current paper highlights important updates to animal models, the role of the environment in shaping choice, and how these models can be used to investigate comorbid conditions.

Animal Models of Gambling-like Behavior

A core feature of animal models of risky decision-making is their heterogeneity; there is no “gold standard” as in related fields like impulsive decision-making (i.e., delay discounting) [1]. Although there are considerable differences between tasks, all of them include the probabilistic delivery of reinforcers and/or punishers. In regard to punishers, choices may involve risk of timeout, shock, unpalatable food, or loss of tokens, whereby reinforcers may vary in probability, modality, and/or amount (for review, see [2, 3]). Moreover, while lack of standardization has been critiqued in science, this variability between behavioral parameters has the potential to yield much stronger inferences from common findings and identify critical controlling environmental variables that influence risky decisions. When considering the variety of models for investigating gambling-like behaviors, the differences between species are of particular interest. Many phenomena have been identified in humans, which ultimately are replicable in various animals. However, animals differ in the degree to which the human condition may be recapitulated.

Pigeons, though not a widely used model for the study of neurobiology, mimic many of the behavioral aspects of humans’ reported gambling experiences. In particular, suboptimal choice/bias (i.e., choosing an option with lower rates of reinforcement) can be reliably induced in pigeons. A relatively common paradigm involves choice between a certain alternative (100%) with a relatively higher reinforcement rate versus a probabilistic alternative (e.g., 50%) with a lower rate of reinforcement. This effect is particularly robust and, in a recent study, was maintained even when choice was made more effortful or when contingencies between the two options were made more discriminable [4].

In contrast to pigeons, rodents are widely used to study the neurobiology of decision-making and are often considered great optimizers, thus they may be less prone to suboptimal decisions. Under an adaptation of the suboptimal choice procedure described above, rats generally tracked overall reinforcement rates [5]. Despite such evidence, there is individual variability in the risky decision-making of rats, and poor decisions can be reliably induced using a variety of environmental or neural manipulations (see more below). Mice follow

¹A PubMed search, conducted for the period of January 2017 through July 2019¹, yielded 141 results, of which 68% were relevant to the current topic. Search terms: (gambling OR gamble OR risky decision-making OR probabilistic decision-making) AND (rat OR mouse OR pigeon OR nonhuman primate) NOT Gamble[au] NOT toxicology.

similar decision-making trajectories to rats, but open up more opportunity for investigation into the genetics of risk-based decisions [6].

Finally, nonhuman primates, although expensive to work with, provide unique opportunities for research into decision-making given that many complex discriminations can be acquired rapidly, leading to a large bank of potential conditions that can be assessed. Moreover, it was recently demonstrated that gambling-like behaviors, including suboptimal decisions, are common across a variety of primate species, including monkeys, gorillas, and orangutans [7].

Species differences are a critical consideration when choosing a model for investigating decision-making under risk. It should be noted that while some differences may be attributed to behavior/training (e.g., stimulus salience) rather than genetics [8], they are rooted in physiological disparities (e.g., dependence on visual stimuli in pigeons versus rats). Moreover, when considering the translational validity of an animal model, species such as rodents may be desirable given that a relatively small portion display aberrant decision-making process, much like humans. However, model choice will depend on the fundamental questions from the researcher. Ultimately, rodents likely represent an ideal species for investigating perturbations to optimal behavior, pigeons for manipulating suboptimal behavior, and nonhuman primates somewhere between these options.

Environmental Determinants of Choice Behavior

Although initial research into risk-based decision-making was primarily concerned with developing appropriate readouts in animal models, recent studies have sought to more closely model the human condition. For instance, in human gambling, considerable audiovisual cues are often present. Consider a typical casino – a host of machines and tables, each associated with a din of noise and flashing lights. Moreover, in the case of video gaming and traditional slot machines, these stimuli are directly paired with winning outcomes. To better understand the influence of these cues, researchers have adopted two major approaches: one in which cues in a single modality (e.g., visual) are paired with specific outcomes, and another in which complex multisensory cues are associated with (typically) larger/riskier reinforcement options.

Pigeons show some degree of preference for a 50% versus 100% probability of reinforcement delivery, even if reinforcer magnitudes are equivalent. A series of recent studies by the Beckmann and Zentall laboratories demonstrated that cue presentation is critical to drive such maladaptive choice behavior. In particular, less predictable [9] or briefer [10] cues associated with suboptimal options lead to greater preference for those. These cues lead to maintenance of suboptimal choice in pigeons, even when reinforcement probabilities were brought as low as 6.25% [11]. Notably, these effects are replicable to some degree in rats as well. Rats prefer a probabilistic cue when outcomes are equivalent, and this bias is maintained even as the choice is made suboptimal [12]; this effect is particularly robust for spatial over visual cues (i.e., lever position). Despite this, other labs have reported that if two (auditory) cues are given to predict probabilities, rats follow more optimal choice patterns [13], suggesting that the influence of cues may depend on how they

are associated with outcomes. Moreover, rats, much like humans, become more risk averse as the magnitude of the reward increases, even when expected values are equivalent [14, 15].

Putatively, additional cues should facilitate the discrimination of contingency outcomes, although the opposite is often observed. In a recent line of research, the Winstanley lab established that complex and variable multisensory cues may actually drive maladaptive choice behavior on a four-choice probabilistic task [16–19]. Given that rats are generally considered optimal responders, this effect has presented a unique opportunity to investigate neurobiological contributors to risky decision-making. For instance, antagonism of the serotonin 2C receptor only affected decision-making in the cued condition [17], while D2/3 receptor agonism via chronic ropinirole administration had no effect on choice [19]. Moreover, large-scale monoaminergic disruption via cocaine self-administration selectively impaired decision-making of the riskiest rats in the cued condition [18, 20]. These experiments illustrate the difficulty in parsing the complex neurobiological mediators maintaining risky decisions and highlight the need for additional research into this area.

While the complexity of these studies and the multiple choice options make it difficult to tease out pure effects of multisensory cues, a recent set of studies has addressed this issue with a two-choice paradigm [21, 22]. In these studies, multisensory cues were presented concurrent with reinforcer delivery, but also introduced during the presentation of suboptimal reinforcers or contingency degradation, a phenomenon described in humans as “losses disguised as wins”. Both studies found shifts to suboptimal alternatives as a result of introducing these cues, suggesting that the cues themselves drive maladaptive decision-making processes. However, the specifics of how this occurs remains to be seen.

Although a large focus has been given to cues in the environment, it should be noted that even merely engaging in behaviors involving probabilistic reinforcement increases preference for riskier reinforcement alternatives. This was demonstrated by exposing rats to a response-dependent probabilistic schedule of reinforcement (variable ratio [VR] schedules) and subsequently testing them on a rodent version of the Iowa Gambling Task [23]. Rats exposed to the VR schedule made more risky decisions and had greater locomotor sensitization to amphetamine, compared to those in a fixed-ratio control group. A second control group, with reinforcer delivery yoked to those in the VR condition, also demonstrated increased risky decisions and locomotor sensitization effects, suggesting that mere exposure to uncertainty may contribute to suboptimal decision-making. This may also drive the interaction with cues as this type of variability will also augment sign-tracking behaviors towards cues [24] as well as promote larger dopaminergic and motoric responses to stimulant drugs [25]. As a whole, these studies illustrate the power of environmental variables, similar to those present in casinos, in promoting maladaptive decision-making. However, these animal models also provide a promising avenue for the testing of pharmacotherapies as well as behavioral interventions that may reduce risk or severity of gambling disorders.

Comorbid Conditions and Underlying Neurobiology

One of the most interesting recent developments in animal models of risky decision-making is their application to the study of psychiatric disorders and neurological diseases. In humans, risky decision-making is associated with a variety of conditions, leading to fundamental questions about the role of maladaptive choice behavior in the development or maintenance of disease states. Perhaps most notable is the degree to which risky decision-making is present in individuals with substance use disorders [26], although other conditions such as acquired brain injuries also considerably alter decision-making process [27]. However, even less substantial challenges to physiology can affect decision-making, and animal models may be used to investigate these.

The literature on addiction is one of the largest subfields to integrate assessments of risky decision-making into animal models. These studies have focused primarily on stimulants such as cocaine and amphetamine, but some literature also exists on alcohol-induced changes in decision-making. Interestingly, the consensus from recent animal literature suggests that risky decision-making is not predictive of initial drug intake or escalation as has been found in impulsive behaviors. Instead, several studies suggest an interaction wherein the behavior of poorly-performing animals may be exacerbated by exposure to psychostimulants (Figure 2A) [18, 20]. Moreover, these increases in impairment are also associated with increased cocaine-seeking or resistance to extinction [20, 28]. Interestingly, these effects may not be dependent on voluntary drug consumption as animals injected daily with cocaine also show shifts to poorer decision-making [29]. One study provides contrary data (more optimal decisions predicting cocaine intake), however, a larger magnitude effect was also found for sucrose self-administration [30]. Together, these studies suggest that vulnerabilities do exist, but may not necessarily predispose drug-seeking behavior unless extensively exposed to a stimulant, and that more work is needed to reconcile the limited conflicting results.

Brain injuries, in the form of strokes or focal trauma have been known to induce risky decision-making in patients for some time [27] and were often considered an exclusion criterion for many studies of risky decision-making or problem gambling. However, until recently, large-scale cohort data on the incidence of gambling disorder in brain-injured populations had been unavailable. Brain damage was recently estimated to increase the risk for gambling disorder 1.2 – 2.8-fold [31, 32], and may go up further with subsequent injuries. Despite the relevance to human patients, animal literature in this realm has been limited, with only two studies to date. In one study, rats with a frontal brain injury showed reduced optimal decision-making on a four-choice probabilistic task, but the shift in preference was spread among both risky and suboptimal (but safe) choices (Figure 2B)[33]. Of note, this pattern of decision-making was present regardless of whether rats learned the task *de novo* after injury or had stable patterns prior to injury. In another study, when rats were exposed to variable reinforcement prior to injury, all rats performed suboptimally, similar to effects described in the Environmental section above, and the effects of brain damage were masked [34]. These data suggest that risky decision-making tasks may be efficacious for assessing therapeutics for populations with brain injury, but that interactions

with environmental variables (e.g., pre-injury learning) may have considerable effects and should be taken into account when considering translation.

Many other conditions exert effects on risk-based decisions, although they may not be as extreme as in the case of substance dependence or brain damage. Of particular interest are challenges that occur during the juvenile period as these may have enduring effects on decision-making well into adulthood. However, most recorded effects have been relatively subtle in nature. For instance, a rather simple manipulation examining the effect of age at acquisition of a four-choice gambling task revealed that motor impulsivity was affected by age (PND 70 vs. PND 90), but not choice behavior [35]. Even larger manipulations, such as adolescent administration of methylphenidate (PND 38–57), intermittent ethanol administration (PND 30–46), or an acute stressor of maternal deprivation (PND 3) also did not affect risky decision-making (Figure 2C), despite methylphenidate causing an increase in choice impulsivity, alcohol causing a pronounced increase in choice latency, and maternal deprivation causing subtle hippocampal-related deficits [36–38]. Despite all of this, some early life manipulations do alter decision-making. Specifically, introduction of a cage-mate during acquisition of a risk discounting task in juvenile rats (PND 36) led to increased tolerance for risk, but had no effect in older rats (PND 70) that had already learned the task [39].

Conclusions

While there is obvious growth and promising new applications in risk-based decision-making (Figure 1), several factors need to be considered in research going forward. One potential problem which is common across many recent papers (and not limited to this subfield) is the dichotomization of populations. It is not uncommon to see animals split into “good and bad” deciders, or “safe and risky”. While convenient, this may artificially mask true relationships in these behaviors that depend on biological variables (e.g., hormone levels, receptor density) which exist on a spectrum. By splitting around the mean or median to generate groups, both type I and type II errors are increased [40]. This risk may be mitigated by taking upper and lower quantiles (commonly 25% or 33%), but a regression-oriented approach to continuous variables should provide stronger explanatory power if a continuous relationship truly exists. Another challenge is one that the whole of animal science is confronting: the lack of females in studies. Recently, studies have demonstrated sex differences in risky decision-making [41, 42], potentially mediated by differences in dopaminergic signaling, making this a priority area for the field. Given the wide variety of animals (pigeons to primates to rodents) that are used, there is robust opportunity to investigate sex differences across a number of models/species.

There are also large opportunities for growth in this subfield which may yield insights into a host of disorders which characteristically present impaired decision-making. In particular, therapeutic agents which are screened in these models may have translational relevance for conditions such as brain injury or addiction. In addition, the advent of highly specific opto- and chemo-genetic interventions, allow investigation into the underlying neurobiology in a manner which was not possible with classic behavioral pharmacology. In particular, tasks with several discrete phases (e.g., initiation, option presentation, choice, outcome)

provide specific points at which individual regions and neurotransmitter systems can be driven/suppressed to gain better understanding of the process by which these decisions are made. These discoveries will then further fuel the ability to understand, and potentially treat, comorbid conditions.

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Highlights

- Animal models are robust for investigating risk-based decision-making
- Environmental factors are key to the development of decision-making patterns
- Risk-based decision making can be used to investigate comorbid disorders

Figure 1. PubMed Results for Animal Models of Gambling. Although still a small subfield, the past decade has had a sharp uptick of interest, with a 2.5-fold increase in current publications relative to 10 years ago (* = including projections through the end of 2019).

Figure 2.

Animal models to investigate comorbid conditions affecting risk-based decision-making. A) Cocaine self-administration worsens decision-making in rats already biased toward risk. Adapted from Ferland & Winstanley [20], with permission. B) Traumatic brain injury (TBI) induces a long-lasting reduction in optimal decision-making. Adapted from Shaver et al. [33], with permission. C) Maternal deprivation does not significantly affect decision-making, despite hippocampal effects (not shown). Adapted from Loi et al. [36], with permission.