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Using rodent models to understand interactions between gambling and substance use

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Abstract

Substance use is strongly associated with gambling, but the nature of this association can be difficult to determine. Rodents offer the opportunity to test causal models of these relationships through isolation of individual variables of interest. This review describes recent research in rodents showing: a) predisposing factors for both gambling-like behavior and substance use; b) exposure to drugs of abuse increasing gambling-like behavior; c) experience with gambling-like behavior increasing substance use; and d) links between gambling-like behavior and substance use in models of Parkinson's disease therapies. These findings reveal novel relationships between gambling and substance use, and highlight the utility of rodent models for future work in this area.

Keywords

Gambling; substance use; addiction; rats; rodents; risk taking

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None

Introduction

As will be familiar to anyone who has walked through a casino, gambling and substance use are tightly linked. It is estimated that 35-75% of individuals who experience problematic gambling have a comorbid substance use disorder (SUD) [1,2], and each condition has the potential to exacerbate the other (e.g., via intoxication leading to excessive gambling, or through use of substances to alleviate anxiety associated with gambling losses). Despite these strong associations, it can be difficult to determine whether substance use is a cause, consequence, and/or correlate of gambling, given the challenges inherent in working with human subjects in cross-sectional or retrospective study designs. Many of these challenges have been circumvented through work in rodents in combination with sophisticated behavioral tasks that model different facets of gambling behavior. In this article, we review research that has used rodents to investigate relationships between gambling and substance use, focusing particularly on findings in the past 5 years.

Associations between gambling-related behavior and substance use

Problematic gambling and substance use share multiple behavioral features [1], suggesting that common characteristics could account for some of their comorbidity. Recent work in rats shows that excessive risk taking, a hallmark characteristic of pathological gambling [1], is strongly associated with drug-related behavior. Using a rat model of the Iowa Gambling Task, Ferland and Winstanley reported that pre-existing risk preference strongly predicted subsequent cocaine-seeking behavior [3]. In this task, rats choose between four options: two associated with large rewards but larger losses (disadvantageous options) and two associated with small rewards but smaller losses (advantageous options). Rats that exhibit an exaggerated preference for the disadvantageous options at baseline later exhibit greater drug-seeking during a test of relapse/reinstatement, compared to rats that exhibit more advantageous choice behavior. This finding echoes previous work in rats showing that greater preference for a large, probabilistically punished food reward over a small, safe food reward (greater risk taking) during adolescence predicts greater cocaine intake during acquisition of cocaine self-administration in adulthood [4]. A similar relationship was recently extended to nicotine-related behavior. Gabriel et al. [5] showed that greater risk taking is associated with greater locomotor sensitivity to first-time nicotine exposure, a measure shown to reliably predict development of nicotine dependence [6,7]. Together, these studies suggest that the excessive risk-taking characteristic of pathological gambling may also be a predisposing factor for development of SUDs.

In addition to maladaptive risk taking, recent rodent data suggest that enhanced sensitivity to reward-predictive cues may facilitate both gambling and substance use [8]. Rats that predominantly approach and interact with a cue predictive of a food reward (i.e., “sign trackers” [9]) make more risky and impulsive choices compared to rats that predominantly approach the location of food delivery (i.e., “goal trackers” [10]). In addition, several recent studies report that individual differences in sign vs. goal tracking are predictive of drug-related behavior in rats. Versaggi et al. observed that sign trackers work harder to self-administer nicotine and exhibit greater cue-induced reinstatement of nicotine-seeking behavior compared to goal trackers [11]. In a separate study, Tunstall et al. [12] showed that,

when given a choice between cocaine and food, sign trackers, but not goal trackers, largely choose cocaine. These recent findings are consistent with earlier work showing that, relative to goal trackers, sign trackers are more likely to engage in cocaine-seeking despite punishment [13], display greater cue-induced reinstatement of cocaine-seeking [14], and invest more effort in obtaining cocaine [15]. It is thought that these individual differences in cue sensitivity (and/or responsivity) reflect differences in the propensity to attribute motivational value to reward-predictive cues, such that in sign trackers, the cue itself gains greater control over behavior [16]. Hence, the hypersensitivity to reward cues reported in individuals with both problematic gambling and SUDs could be due to exaggerated attribution of incentive value to such cues, which in turn drives and maintains both gambling and substance use [8,17–19].

Exposure to drugs of abuse exacerbates gambling-like behavior

Rodent models have been instrumental in demonstrating causal relationships between exposure to drugs of abuse and alterations in cognitive functions relevant to gambling, including executive functions, risk taking, and impulsivity (e.g., [20–23]). Assuming similar cognitive alterations occur in humans, they could potentiate vulnerability to problematic gambling, and potentially fuel a “vicious cycle” in individuals already predisposed to both substance use and gambling (see previous section). Much of the work in this area has focused on cocaine. For example, two weeks of long-access cocaine self-administration causes an enduring increase in preference for large, probabilistically punished over small, safe rewards, in comparison to a control group with comparable experience self-administering an oral sucrose solution [4]. A similar experimental design was used to show that self-administered cocaine causes an enduring increase in preference for small, immediate over large, delayed rewards in an intertemporal choice task [24]. More recently, Ferland et al. [3] showed that chronic cocaine self-administration exacerbates decision-making deficits in rats that preferentially choose disadvantageous options in a rat gambling task, and that these exacerbated deficits persist well into abstinence. Decisionmaking deficits have also been observed following exposure to other drugs of abuse. Rats given daily injections of methamphetamine followed by two weeks of abstinence preferentially choose riskier options (large reward/high probability of punishment vs. small reward/low probability of punishment) compared to vehicle-injected rats [25,26]. Finally, chronic voluntary alcohol consumption increases risky choice in a probability discounting task in which rats choose between a small certain reward and a large reward [27]. Notably, this increase in risk taking is only evident in rats exposed to alcohol during adolescence and not adulthood, indicating a critical window of vulnerability in which alcohol can cause lasting changes in decision making.

Experience with gambling-like behavior promotes substance use

Exposure to gambling opportunities, such as electronic gambling machines and online gambling, is associated with dysregulation in mesolimbic dopaminergic circuitry similar to that induced by psychostimulant exposure. A key component of gambling, exposure to uncertain rewards, has recently been promoted as a primary mediator of this process, and work using animal models has sought to understand how exposure to uncertainty affects

responses to psychostimulants and drug-seeking behavior [28–30]. Much of this work has involved comparisons of the effects of prior experience with fixed ratio (FR) vs. variable ratio (VR) schedules of reinforcement. For example, Mascia and colleagues [31] trained rats to nosepoke for saccharin reward on either a FR or VR schedule, then tested their willingness to self-administer amphetamine as well as their sensitivity to passive amphetamine exposure. Rats trained under the VR schedule self-administered more amphetamine than rats trained under the FR schedule. The VR group also exhibited greater amphetamine-induced locomotor activity and nucleus accumbens (NAc) dopamine efflux, the latter of which is associated with drug craving and compulsive gambling [32,33]. Such sensitization to the effects of amphetamine is also observed following repeated psychostimulant exposure [34], suggesting that intermittent striatal dopamine release, be it from exposure to uncertainty or drugs of abuse, may drive neural adaptations that promote risky behaviors including both gambling and substance use.

The Mascia et al. study (as well as actual gambling) involves volitional behavior; however, it appears that even passive exposure to uncertainty can contribute to psychostimulant sensitization. Zeeb et al. [35] compared amphetamine-induced locomotor sensitization in rats that earned sucrose rewards on a FR20 or VR20 schedule with rats that passively received the same reward on a schedule yoked to the VR group. Consistent with the findings of Mascia et al., amphetamine-induced dopamine efflux in the NAc was greater in the VR than the FR group. Dopamine efflux was also elevated in the passive group though, suggesting that experience with uncertain rewards can sensitize mesolimbic dopamine signaling even in the absence of instrumental action. These studies together show that exposure to uncertainty may sensitize the same behavioral and neurobiological mechanisms that are hijacked by drugs of abuse. The comorbidity between SUDs and problematic gambling may be mediated by sensitization to the same regions of the brain, with the element of uncertainty being the central driver of gambling-related sensitization [30].

Gambling-like behavior and substance use in rodent models of Parkinson's disease and Parkinson's disease treatment.

Impulse control disorders (ICDs), including problematic gambling, are associated with dopaminergic therapies for Parkinson's disease (PD), potentially providing insight into relationships between gambling and substance use [36,37]. In the classic model of basal ganglia motor control, dopamine impinges on both the 'direct' and 'indirect' pathways for motor function, resulting in an increased or decreased likelihood of movement, respectively. A similar go/no-go model informs theories of dopaminergic modulation of motivation and reward, with activity at D1 receptors signaling positive reinforcement and pauses in activity at D2 receptors signaling punishment [38,39]. According to this model, chronic administration of exogenous dopaminergic medications (or drugs of abuse) increases tonic D1 tone, leading to greater positive reinforcement for novel stimuli. At the same time, and particularly with D2/D3 agonists (which have the further effect of desensitizing D2 autoreceptors), pauses in activity at D2 receptors are attenuated. This combination of enhanced signaling of positive reinforcement and attenuated signaling of punishment is thought to underlie development of ICDs in patients taking dopaminergic medications for

PD [40,41]. In support of this idea, recent rat studies show that chronic administration of the D2/3 agonists ropinirole [42–44] or pramipexole [45,46] increases impulsivity and gambling-relevant choice behavior in both intact and PD model rats.

An important pathologic feature of PD involves degeneration of striatal dopaminergic input in a caudo-rostral pattern, with the posterior (sensorimotor) putamen affected first, resulting in relative sparing of limbic circuits. As a result, dopaminergic medications may overstimulate limbic dopamine receptors for a given therapeutic motor benefit in PD, resulting in ICDs [46–48]. In an analogous manner, a genetic imbalance of D1 vs. D2/D3 receptor activity could predispose individuals to risk-taking/gambling, which could be exacerbated by substance use and potentially create a positive feedback loop leading to increases in both behaviors [49]. Such pathology- or genetically-induced shifts in striatal dopamine signaling would be expected to interact with D2/D3 agonist medications. Given the alterations in choice behavior induced by these medications in intact rats, however [42–46], such shifts in dopamine signaling are likely not required.

Deep brain stimulation (DBS) is growing in use as a treatment for PD as well as other movement disorders, and recent work in rodents suggests that it lacks some of the liabilities of dopamine agonists. Indeed, DBS targeting the subthalamic nucleus attenuates risk taking in a rat gambling task, particularly in rats that innately preferred high-risk options [50]. This same approach was shown in previous work to reduce cocaine-seeking, suggesting that DBS of the subthalamic nucleus, as well as other brain structures, could prove useful in treating both problematic gambling and substance use [51–53]

Conclusions

Recent work using rodent models provides clear evidence for strong, multi-directional connections between substance use and several aspects of gambling-like or gambling-relevant behavior (Figure 1). Despite these advances, however, there are several areas in which current research has been limited. First, the majority of work involving self-administered drugs of abuse has focused on cocaine. Although cocaine is still a significant (and growing) public health concern, there have been few studies of more prevalent drugs of abuse such as nicotine, cannabis, and opioids. Second, most work to date has been descriptive rather than mechanistic. Although it is clear that alterations in dopamine signaling play a significant role in gambling-substance use associations, the contributions of other components of the limbic-striatal networks that govern each aspect of behavior individually have yet to be thoroughly explored. Finally, as is the case in most areas of neuroscience, almost all preclinical research on links between gambling and substance use has employed male rats. Given the small but growing literature demonstrating robust sex differences in each aspect of behavior separately [54,55], it is incumbent upon the field to employ both male and female subjects in future studies of gambling-substance use associations.

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Highlights:

- Individual rats show predispositions to both gambling-like behavior and substance use
- Chronic substance use in rats can exacerbate gambling-like behavior
- Experience with gambling-like behavior can facilitate substance use
- Parkinson's disease and its treatments can interact with gambling-like behavior

Figure 1:
Illustration of interactions between substance use and gambling-like behavior in rodent models described in the text.