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Review

# Neural mechanisms regulating different forms of risk-related decision-making: Insights from animal models

Caitlin A. Orsini[a,1], David E. Moorman[b,1], Jared W. Young[c,d], Barry Setlow[a], Stan B. Floresco[e,*]

[a] Department of Psychiatry and Center for Addiction Research and Education, University of Florida College of Medicine, Gainesville, FL, United States
[b] Department of Psychological and Brain Sciences, University of Massachusetts, Amherst, MA, United States
[c] Department of Psychiatry, University of California San Diego, United States
[d] VISN-22 Mental Illness, Research, Education and Clinical Center (MIRECC), VA San Diego Healthcare System, San Diego, CA, United States
[e] Department of Psychology and Brain Research Center, University of British Columbia, Vancouver, BC, Canada

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ABSTRACT

Over the past 20 years there has been a growing interest in the neural underpinnings of cost/benefit decision-making. Recent studies with animal models have made considerable advances in our understanding of how different prefrontal, striatal, limbic and monoaminergic circuits interact to promote efficient risk/reward decision-making, and how dysfunction in these circuits underlies aberrant decision-making observed in numerous psychiatric disorders. This review will highlight recent findings from studies exploring these questions using a variety of behavioral assays, as well as molecular, pharmacological, neurophysiological, and translational approaches. We begin with a discussion of how neural systems related to decision subcomponents may interact to generate more complex decisions involving risk and uncertainty. This is followed by an overview of interactions between prefrontal-amygdala-dopamine and habenular circuits in regulating choice between certain and uncertain rewards and how different modes of dopamine transmission may contribute to these processes. These data will be compared with results from other studies investigating the contribution of some of these systems to guiding decision-making related to rewards vs. punishment. Lastly, we provide a brief summary of impairments in risk-related decision-making associated with psychiatric disorders, highlighting recent translational studies in laboratory animals.



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* Corresponding author at: Department of Psychology and Brain Research Center, University of British Columbia, 2136 West Mall, Vancouver, BC V6 T IZ4, Canada. Tel.: +1 604 827 5313; fax: +1 604 822 6923.
*E-mail address:* floresco@psych.ubc.ca (S.B. Floresco).
[1] These authors contributed equally to this work.

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Cost/benefit decision-making is a fundamental executive process that is common across species, ranging from worms, rodents, non-human primates and of course, humans. In particular, all organisms are faced on a daily basis with choices between options that differ in their expected reward and potentially negative consequences that may accompany those rewards. Thus, a system that integrates information related to risk and reward, as well as internal motivational drives and environmental factors, is crucial to be able to make adaptive decisions and guide subsequent behavior. In humans, most individuals are able to calculate the relative costs and benefits of options and make appropriate choices; however, maladaptive decision-making is a behavioral hallmark of several psychiatric conditions. For example, individuals diagnosed with substance use disorders display an increased propensity to engage in risky behavior, such as unprotected sex and intoxicated driving (Lejuez et al., 2005; Pulido et al., 2011). Other psychiatric conditions, such as anorexia and schizophrenia, are characterized by a pathological decrease in risk-taking behavior (Kaye et al., 2013; Reddy et al., 2014). Thus, a better understanding of the neurobiology underlying normal risky decision-making will provide insight into how these processes may go awry in pathological conditions.

Seminal work by Bechara and colleagues provided the first neurobiological clues as to how the brain mediates decision-making under risk. Using what has become a well-established behavioral assay of risky decision-making, the Iowa Gambling Task (IGT), Bechara et al. (1994, 1999) demonstrated that patients with prefrontal cortical damage were impaired in this task. In the IGT, subjects are asked to choose between different decks of cards, which differ in their long-term profitability. While healthy subjects choose cards that yield longer term payoffs, patients with prefrontal damage [encompassing the ventromedial and orbitofrontal (OFC) subregions] choose cards that yield a large immediate gain, but are accompanied by even larger losses in the long-term, indicating that damage to this brain region increases risky choice. Further insight into the role of the prefrontal cortex (PFC) in risky decision-making derives from more recent neuroimaging experiments in subjects diagnosed with psychiatric conditions characterized by pathological risk-taking behavior. Several studies have shown that substance abusers exhibit hypoactivation of various subregions of the PFC during decision-making (Fishbein et al., 2005; Crowley et al., 2010) and that this decreased functional activity is associated with preference for risky choices (Fishbein et al., 2005). Similarly, adults with attention deficit hyperactivity disorder (ADHD), a condition also associated with elevated risky decision-making (DeVito et al., 2008; Klein et al., 2012), have less extensive activation of the PFC relative to controls during risky decision-making (Ernst et al., 2003).

The PFC, as well as other brain regions implicated in risky decision-making, receives robust dopaminergic input from the ventral tegmental area (VTA). As such, alterations in dopamine (DA) signaling may have a deleterious impact on decision-making under risk. This is indirectly supported by studies that have assessed decision-making in individuals suffering from psychiatric conditions in which perturbations in the dopaminergic system are thought to be an underlying cause. For instance, stimulant abusers, schizophrenics, and patients with ADHD display maladaptive risky decision-making both in real world measures (Friedman, 1998; Lejuez et al., 2005; Klein et al., 2012; Ramos Olazagasti et al., 2013) and when assessed in laboratory gambling tasks (Rogers et al., 1999b; Bornovalova et al., 2005; Leland and Paulus, 2005; Schneider et al., 2012). As further evidence, when treated with DA agonists, patients with Parkinson's disease and Restless Legs Syndrome can develop increased risk-taking (Dagher and Robbins, 2009), clearly indicating a role of DA in modulating risk-based decision-making. Finally, more recent studies have shown that poor performance in the IGT in pathological gamblers is associated with increased DA release in the ventral striatum (Linnet et al., 2011a,b). Altogether, these studies reveal the important contribution of the dopaminergic system to risky decision-making, and suggest that dysregulation in this system is a major cause of pathological risk-taking.

While informative, studies in humans are limited in their ability to determine how specific brain regions, and in particular, how neurochemical signaling within these regions, facilitate different component processes related to decision-making. Animal models have allowed researchers to address fundamental questions about the neural mechanisms supporting different forms of risky decision-making and how these systems may be impacted in pathological states. Critical to these questions, however, is understanding how different behavioral and cognitive elements of decision-making sculpt subsequent behavior. For example, making a decision between multiple options entails consideration of past outcomes, the relative value of the benefits associated with each option, and the valence and type of risk that may accompany those options, all of which must be integrated with other environmental and motivational factors in order to execute or inhibit behavior. The main endeavor of this review is to describe these processes and to highlight recent animal studies investigating the neural bases of different forms of risk-based decision-making. It begins with a discussion of the basic cognitive and neural systems underlying decision-making behaviors, followed by reviews of the neurobiology of two distinct animal models of decision-making involving different types of uncertainty or risk. Finally, the review extends this discussion to psychiatric conditions characterized by impaired risk-based decision-making, and highlights the necessity of assessing different components of decision-making so as to gain a more comprehensive understanding of these disorders.

## 1. Decision making is supported by multiple, diverse neural systems

As alluded to previously, decision-making encompasses a complex conjunction of many behaviors. This is exemplified by the fact that there is an entire field related to sensorimotor decision-making, a close cousin of the type of motivational decision-making addressed here. The framework for sensorimotor decision-making is frequently rooted in neurophysiological studies, in which temporal components of behavior are well-controlled. These studies focus on the accumulation of information that ultimately allows a decision to be made and a response to be executed. For example, many studies have investigated decisions related to ambiguous visual stimuli, such as a field of dots in which some percentage (0–100%) is moving coherently in one direction while the others are moving randomly (Shadlen and Newsome, 1996). Subjects in this