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## The Importance of Animal Models of Decision-Making, Gambling and Related Behaviors: Implications for Translational Research in Addiction

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Addictions are arguably the most costly medical disorders, with annual costs to US society estimated to exceed \$500 billion dollars and be larger than those associated with stroke, heart disease and diabetes combined (Uhl and Grow, 2004). Despite the immense costs associated with addictions, relatively few effective treatments exist, particularly for specific addictions like cocaine dependence for which no pharmacotherapies are currently approved by the US Food and Drug Administration. As such, there exists a significant need for more research into the etiologies and neurobiologies of addictions such that more effective treatment strategies may be developed for these currently costly disorders. Given that addictions, like other psychiatric disorders, are complex processes whose etiologies likely involve multiple genetic and environmental determinants that interact in a dynamic manner, using multiple approaches and disciplines in an integrative fashion will be important in order to make substantial inroads into our understanding of addictions and translate this knowledge into prevention and treatment advances.

Addictions have been conceptualized as disorders of misdirected motivation in which one typically hedonic and maladaptive behavior (e.g., drug use) takes precedence over other more adaptive ones (e.g., performing well at work or attending to familial concerns) (Potenza, 2006). This conceptualization is consistent with descriptions of the core components of addictions that typically include an element of continued engagement in a behavior despite adverse consequences (Potenza, 2006). Consistently, much research over the past decade has involved assessments of decision-making in individuals with addictions (Bechara, 2003). Neuroeconomic paradigms have investigated temporal discounting of monetary rewards (as well as drug rewards) in individuals with addictions and have found that individuals with addictions tend to discount rewards more rapidly than those without addictions, and that the discounting behaviors are associated with clinically relevant features like treatment outcome (Krishnan-Sarin *et al*, 2007). More complex paradigms, like the Iowa Gambling Task (IGT) that involves risk-reward decision-making coupled with the learning of a strategy that is not intuitively obvious, have also demonstrated deficits in individuals with addictions (Bechara, 2003). Moreover, an association between IGT performance and real-life measures of functioning (e.g., ability to hold a job) has been reported in addicted individuals, highlighting the real-life relevance of performance on this task (Bechara, 2003). As such, an improved understanding of the neurobiology of decision-making holds significant promise for generating clinical advances for the prevention and treatment of addictions.

Precisely how decision-making is related to addiction remains relatively poorly understood. That is, individual differences in decision-making may relate to genetic and/or early life

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environmental factors, or their interactions, and may exist prior to the drug exposure experienced in drug addictions. Alternatively and not mutually exclusively, drug exposure may influence the neural structures and functions underlying decision-making. Animal models are important in investigating these questions, and animal data indicate roles for each possibility. For example, in the first instance, individual differences in impulsivity prior to drug exposure have been linked to drug use behaviors. In a model of cocaine dependence, response impulsivity predicted compulsive drug use (Belin *et al*, 2008), and in investigations of nicotine administration, response impulsivity predicted enhanced motivation to initiate and maintain nicotine self-administration and impulsive choice on a delayed reward task predicted re-initiation of nicotine use following abstinence (Diergaarde *et al*, 2008). With respect to the second possibility, alcohol exposure during adolescence has been found to lead to risky decision-making later in life (Nasrallah *et al*, 2009), indicating that both individual differences in decision-making prior to substance exposure and substance exposure itself (as well as the timing and duration of such) are important considerations in addictions. These animal studies, that include pre-drug-exposure assessments, controlled experimental conditions, longitudinal characterization, and (in some cases) non-drug-exposed experimental groups, provide important information that could not be obtained in human studies due to lack of feasibility. As such, they offer a critical complement to human investigations.

The recent investigation by Zeeb and colleagues (Zeeb *et al*, 2009), as well as another recent one by Rivalan and colleagues (Rivalan *et al*, in press), models the IGT in rats. Both groups use the task to investigate important aspects of decision-making: influences on task performance of serotonergic and dopaminergic drugs and individual differences in reward sensitivity and anxiogenic risk-taking, respectively. Although each study provides important information in its own right, there is significant hope that they represent the initial basis for multiple investigations that de-construct and probe specific aspects of decision-making as related to addiction. As evidenced by other examples above, such investigations could utilize carefully controlled longitudinal experimental conditions that are not practical or feasible in human studies. Such investigations could also utilize additional approaches (e.g., genetic manipulations, proteomic analyses, electrophysiological recordings or neurochemical assessments) that are also typically not feasible in people yet provide important information into neurobiological processes. Additionally, careful coordination between pre-clinical and clinical investigations, such as those that model the same behavior or paradigm (here the IGT) across species could facilitate the translation of information in a manner that could help dissect and clarify complex processes underlying addiction and generate clinical advances. Importantly, the availability of animal models of the IGT also holds promise for better understanding gambling behaviors and human conditions like pathological gambling, for which the lack of availability of appropriate animals models has slowed research into the disorder. As such, these studies hold significant implications of a broad range of neuropsychiatric conditions and thus could contribute to multiple clinical advances that could benefit many individuals, their families, and society as a whole.

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control disorders or other health topics; has consulted for law offices and the federal public defender's office in issues related to impulse control disorders; has performed grant reviews for the National Institutes of Health and other agencies; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; has generated books or book chapters for publishers of mental health texts; and provides clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program.

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