Rolling the Dice: The Importance of Mesolimbic Dopamine Signaling in Risky Decision Making

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To maximize resources, organisms must learn to predict the outcome of various options and choose the most valuable alternative. Behavioral choices such as 'playing it safe' *vs* 'taking a risk' engage a complex circuit that includes the mesolimbic dopamine (DA) system. A seminal study by Schultz *et al* (1997) showed that mesolimbic DA neurons function as a 'teaching signal' and encode cues that predict rewards and errors in those predictions. DA release in the nucleus accumbens (NAc) reflects this learning signal, and also processes information about reward value as animals are actively making decisions. For example, DA release in the NAc core is higher for cues that predict more valuable rewards, and signals the most valuable available option (Day *et al*, 2010).

Organisms rarely encounter situations in which simple stimulus-outcome associations are in effect, and thus must rely on multiple factors to make appropriate decisions including the representations of internal needs and external states, possible courses of action, and the consequences of those actions (Rangel *et al*, 2008). Risky decision making involves this type of complex evaluation and is of particular interest because it is implicated in several psychiatric disorders, including gambling and drug addiction. Risk-taking behavior has been modeled in rats using a task where subjects are allowed to choose between larger more uncertain rewards or smaller certain rewards. Importantly, in this task, it is not more advantageous to make one response over the other, and as such it is possible to evaluate intrinsic subjective value and individual risk attitudes. We have found that DA release in the NAc encodes the subjective value of future outcomes and, when given a free choice, may bias animals toward a risk or safe preference (Sugam *et al*, 2012).

However, the mesolimbic DA-NAc system does not function in isolation. Disruptions of the basolateral amygdala (BLA), prefrontal cortex (PFC) and NAc circuitry have resulted in differential effects on risk-taking. The BLA-NAc circuit appears critical for encoding reward probabilities, thus biasing animals to more valuable options when risks are lower. The PFC appears critical for tracking reward omissions and is important for shifting behavior as rewards become more uncertain and less valuable (St Onge *et al*, 2012). These findings suggest that each discrete region in this larger circuit has different roles in mediating appropriate decision making, and signaling from these structures likely modulate the value signaling of the mesolimbic DA system in risky decision making.

Recent advances in optogenetic techniques allow for the probing of individual portions of the reward circuit in mediating risk-taking behavior. For example, using a genetic line of rats, researchers were able to selectively activate DA fibers arising from the ventral tegmental area and showed that this manipulation is sufficient to drive motivated behaviors (Witten *et al*, 2011). Thus, future studies can apply optogenetic tools to selectively manipulate DA signaling while rats are deciding to engage in risk-taking behavior, and examine the causal relationship between rapid DA signaling in each discrete region of the mesolimbic circuit and risky behaviors. Determining the mechanisms that underlie appropriate risk-taking behavior will not only enhance our understanding of the role of this circuitry in normal decision making, but will also provide insight into what goes wrong during maladaptive risk taking. This approach may help identify optimal targets for therapeutic treatments of maladaptive decision making that occur, for example, in drug or gambling addiction or in eating disorders.

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DISCLOSURE
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Epigenetics of Methamphetamine-Induced Changes in Glutamate Function

Addiction to methamphetamine (METH) is a relapsing neuropsychiatric disorder that is secondary, in part, to functional changes in limbic and striatal brain regions (reviewed in Krasnova and Cadet (2009)). Stimulant-induced plastic changes within the striatum are dependent on a series of events that include modifications in the number and subtypes of glutamate receptors (Wolf and Ferrario, 2010). Elucidating the basic mechanisms that maintain METH addiction is important because such an understanding will probably lead to the development of efficacious treatments. The accumulated evidence supports the notion that illicit drugs exert substantial transcriptional and epigenetic changes in the brain (Robison and Nestler, 2011).