Dopamine Signaling in the Dorsomedial Striatum Promotes Compulsive Behavior

Jillian L. Seiler, Caitlin V. Cosme, Venus N. Sherathiya, Joseph M. Bianco, and Talia N. Lerner

Persevering through difficult circumstances to receive a valuable payoff can constitute adaptive resilience. It can also be maladaptive. For example, pursuing drugs such as cocaine or alcohol when doing so is detrimental to one's well-being is a crucial component of the transition from recreational drug use to the development of substance use disorder (SUD). Although we *cannot* access the inner thoughts of mice, we can use rodents to ask which brain systems (shared across mammalian species) drive a continued engagement in punishment-resistant reward-seeking. A limitation of previous studies on the development of punishment-resistant reward-seeking is an overwhelming focus on *drugs* as reward. Little is known about the development of punishment-resistant reward-seeking more broadly. This gap in knowledge is problematic both for our understanding of addiction (how different is addiction to drugs from "addiction" to overeating, gambling, sex, or video games?) and for our understanding of how punishment-resistant reward-seeking could contribute to other disorders. By studying natural reward-seeking for sucrose, my lab seeks to bring together two fields: one that has put considerable effort into studying punishment-resistant *drug-seeking*, and another that has concentrated on characterizing *basic reward learning mechanisms*. Our data show that punishment-resistant reward-seeking develops in mice after prolonged operant training for sucrose rewards and that there is substantial individual and sex-dependent variation in the course of development. To understand the neural circuits underlying this variation, we have recorded the activity of dopamine axons targeting the dorsomedial striatum (DMS) and dorsolateral striatum (DLS) during learning in both male and female mice. We find that DMS dopamine axon activity predicts which individuals will develop punishment-resistant reward-seeking and that optogenetic manipulations of DMS but not DLS dopamine during learning impact the acquisition of punishment-resistant reward-seeking. These results provide a basis for future work to understand how DMS dopamine circuits may be hijacked by drugs of abuse to produce maladaptive behavior.

This work was supported by an NIH K99/R00 Award (R00MH109569), an NIH Director's New Innovator Award (DP2MH122401), and a NARSAD Young Investigator Award from the Brain & Behavior Research Foundation.