

Submitter name: Drew Kiraly
Submitter email: drew.kiraly@mssm.edu

Manipulations of gut microbiome diversity alter cocaine seeking behavior and striatal gene expression.

Katherine R. Meckel¹, Kelsey E. Lucerne¹, Rebecca S. Hofford², Emily G. Peck³, Arthur Godino¹, Erin S. Calipari⁴, **Drew D. Kiraly**^{1,2}

¹Nash Family Department of Neuroscience, Icahn School of Medicine at Mount Sinai; ²Department of Psychiatry, Icahn School of Medicine at Mount Sinai; ³Department of Physiology and Pharmacology, Wake Forest School of Medicine; ⁴Department of Pharmacology, Vanderbilt University

Addiction to psychostimulants represents a major public health crisis with limited treatment options. Despite tremendous advances in understanding of the neurocircuitry and intracellular signaling cascades altered in models of stimulant use, there are no FDA-approved pharmacotherapies for treatment of cocaine or other stimulant use disorders – highlighting a need for new translational research targets. There is a growing understanding that the resident population of bacteria in the intestinal tract, the gut microbiome, markedly influences brain homeostasis and function in multiple models of neuropsychiatric disease. Our group has previously demonstrated that shifts in the gut microbiome led to enhanced cocaine place preference for low dose cocaine and altered gene expression levels in the brain. Here, we utilized a paradigm of microbiome depletion with oral antibiotics combined with a model of drug self-administration and reinstatement to identify microbiome effects on brain and behavior in a model of relapse. We find that depletion of the gut microbiome increases cue- and drug-induced reinstatement of cocaine seeking after prolonged withdrawal. RNA-sequencing analysis of the nucleus accumbens of animals receiving a cocaine challenge after four weeks of withdrawal demonstrated marked changes in gene expression in the microbiome depleted animals. These changes in nucleus accumbens gene expression are accompanied by alterations in permissive histone acetylation marks and decreased activity of the important activity-dependent transcription factor CREB. These data show manipulations of the microbiome affect long-term plasticity of brain and behavior in animal models of relapse and lay the foundation for future translational research in this area.