

Name: Dmitry Velmeshev, PhD

Email: dmitry.velmeshev@duke.edu

Dissecting and modulating cell type and circuit-specific epigenetic mechanisms of cocaine addiction

Cocaine is highly addictive, and cocaine addiction is devastating to society and individuals, leading to financial loss, job loss and violence within families. Cocaine use especially affects the limbic system, in particular, nucleus accumbens, as well as hippocampus, the amygdala and the prefrontal cortex, leading to changes in activity and long-term rewiring of the circuitry, which causes cocaine craving and addiction. The knowledge of how cell type-specific molecular changes resulting from cocaine use lead to rewiring of circuits relevant to cocaine-seeking behavior is limited. Moreover, treatments of cocaine addiction that prevent drug seeking via restoring the normal states of neurons and circuits that are dysregulated as the result of repeated cocaine use are desperately needed. We will utilize mice repeatedly exposed to cocaine in a well-established conditioned place preference paradigm to investigate cell type and circuit-specific epigenetic mechanisms underlying cocaine addiction. Using a combination of a novel approach we developed called inducible barcoded rabies virus with activity-dependent neuronal tagging and single-cell genomics, we propose to identify epigenetic changes in specific limbic system neuronal cell types and circuits active during cocaine-seeking behavior. We will then test the hypothesis that cocaine-seeking behavior can be erased by performing epigenetic editing of hippocampal neurons projecting to the nucleus accumbens that are active during detection of cocaine-conditioned cues. To that end, we will utilize a novel gene editing tool we developed called CRISRP-rabies to modulate epigenetic states of specific neuron types within defined hippocampal-NAc circuits conditioned by cocaine use. Our study will discover conceptually novel mechanisms of cocaine addiction and will build a foundation for new types of therapies for drug addiction by rewiring specific circuits responsible for drug seeking behavior.

Authors:

Submitter: Dmitry Velmeshev, Assistant professor, Duke University, Durham