Fentanyl abstinence causes neuron subtype specific structural and molecular changes in the nucleus accumbens

Megan E Fox¹, Andreas B Wulff², Cali A. Calarco¹, Makeda D. Turner¹, Daniela L. Franco², Ramesh Chandra¹, Michel Engeln¹, Seth Ament³,⁴, Mary Kay Lobo¹,⁴

¹Anatomy and Neurobiology, University of Maryland School of Medicine; ²Graduate Program in Neuroscience, University of Maryland Baltimore, ³Institute for Genome Sciences, University of Maryland School of Medicine; ⁴Psychiatry, University of Maryland School of Medicine

Opioid abuse has risen dramatically over the last decade. Potent, synthetic opioids like fentanyl are responsible for nearly half of opioid-related deaths, yet synthetic opioid abuse remains broadly understudied. Opioids, like other drugs of abuse, engage and alter dopaminergic circuitry to promote continued use and eventual relapse. Neurons in the Nucleus Accumbens (NAc) play a key role in drug abuse and receive dopaminergic input from the midbrain. NAc medium spiny neurons (MSNs) express either dopamine D1 or D2 receptors, and manipulation of their activity can oppositely regulate drug-related behaviors. Drug-related plasticity in NAc is mainly driven by molecular and structural changes to MSNs, but how synthetic opioids alter specific MSN subtypes remains understudied. Here we show reduced dendritic complexity of D1-, but not D2-MSNs after homecage fentanyl exposure and abstinence that is associated with increased stress-like behaviors. We performed RNA sequencing of the D1- and D2-MSN translatomes, and used weighted correlation network analysis (WGCNA) to identify 11 MSN subtype specific gene networks altered by fentanyl abstinence. We found a cluster of dendritic morphology genes downregulated exclusively in D1-MSNs that are transcriptionally co-regulated by E2F1. Overexpression of E2F1 in D1-MSNs protected mice from abstinence-induced D1-MSN dendritic atrophy and stress-like behaviors. Together, our findings indicate that fentanyl abstinence generates unique structural and molecular changes in NAc MSN subtypes. Our ongoing work aims to characterize the impact of E2F1 overexpression on gene expression and abstinence-induced physiological changes in D1-MSNs.