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Neuron subtype specific structural and molecular changes following fentanyl abstinence

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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. While it is known that morphine exposure causes a loss of dendritic spines on NAc MSNs, it is unknown if this is true for synthetic opioids, and if the changes are specific to D1- or D2- MSNs. Here we show that after homecage fentanyl exposure and abstinence, both male and female mice show increased social-withdrawal and reduced dendritic complexity specific to D1-MSNs. To identify the molecular mechanisms behind cell-type specific dendritic remodeling, we used D1- or A2A-Cre mice crossed with RiboTag mice to isolate ribosome-associated mRNA in specific cell types after fentanyl. We performed RNA sequencing of the D1- and D2-MSN translatome and found >4,000 differentially expressed genes. We used weighted correlation network analysis (WCGNA) to identify 11 cell subtype specific gene networks altered by fentanyl abstinence, including a cluster of dendritic morphology genes downregulated exclusively in D1-MSNs. Ongoing experiments aim to delineate the precise molecular mechanisms underlying the social behavior deficits and neuron subtype specific atrophy after fentanyl abstinence.