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Neuronal activation by cocaine varies across molecularly-defined subpopulations of VTA dopamine neurons

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Substance use disorder is a complex neurobiological disease characterized by a loss of control over drug-taking and drug-seeking behaviors. Drugs of abuse increase dopamine (DA) transmission from ventral tegmental area (VTA) DA neurons that densely innervate the nucleus accumbens. Using single nucleus RNA sequencing, we previously comprehensively profiled the VTA and identified unique markers for two distinct subpopulations of DA neurons. *Slc26a7*, a gene that encodes an anion transporter, serves as a selective marker for combinatorial neurons that express genes implicated in glutamate, GABA, and DA neurotransmission. Likewise, the GTP cyclohydrolase *Gch1* was identified as a marker for DA-only neurons. Here, we used multiplexed fluorescence in situ hybridization to characterize the spatial distribution of the two subpopulations and examine whether distinct DA neuron subpopulations respond differently to drugs of abuse. *Slc26a7*+ cells were found to preferentially reside along the midline of the posterior VTA while *Gch1*+ cells were abundant throughout the VTA and neighboring substantia nigra. Furthermore, we identified unique induction of the neuronal activity marker *Fos* in *Slc26a7*+ cells in the VTA 1-hour following cocaine experience. The same response was not observed in *Gch1*+ cells, suggesting a difference in response to cocaine between these DA subpopulations. Notably, fentanyl administration (or fentanyl and cocaine co-administration) did not significantly elevate *Fos* mRNA in either subpopulation. These results suggest that these two subpopulations of DA neurons within the VTA respond in unique ways to cocaine and may in turn drive distinct downstream effects and behavioral responses to cocaine.