Name: Raleigh Linville Email: linville@mit.edu
PI Name: Myriam Heiman PI email: mheiman@mit.edu

Cellular taxonomy of the human and mouse striatum defines novel neuronal subtypes in opioid and antipsychotic action

Raleigh M. Linville[1,2,*], Benjamin James,[2,3,*] Kiki Galani, [2,3] Jung Hoon Shin[7], Charlotte Wang[1], Sebastian Pineda [2,3] Li-Lun Ho[2,3], Deborah C. Mash[4], Gustavo Turecki[5], Bertha Madras[6], Veronica A. Alvarez[7,#], Dana H. Gabuzda[8, #], Manolis Kellis[2,3, #], Myriam Heiman[1, #]

[1]Picower Institute for Learning and Memory, Massachusetts Institute of Technology; [2]The Broad Institute of MIT and Harvard; [3]Computer Science and Artificial Intelligence Lab, Massachusetts Institute of Technology; [4]Department of Neurology, University of Miami; [5]Department of Psychiatry, McGill University; [6]Department of Psychiatry, Harvard Medical School; [7]Laboratory on Neurobiology of Compulsive Behaviors, National Institute on Alcohol Abuse and Alcoholism (NIAAA); [8]Department of Neurology, Harvard Medical School; *denotes equal contribution; [#]denotes co-corresponding authors

The striatum is the main input nucleus of the basal ganglia, receiving dopaminergic projections from the midbrain and glutamatergic projections from the cortex, amygdala, hippocampus, and thalamus. GABAergic medium spiny neurons (MSNs) integrate these diverse inputs and project to extrastriatal targets, forming circuits with key roles in motor learning, decision making, and reward processing. While imbalanced MSN signaling is increasingly recognized as a key mechanism contributing to substance use disorder and neuropsychiatric disease, a full molecular and spatial characterization of human striatal neurons is lacking. Here, we provide a comprehensive atlas of striatal neuron diversity across 85 single-nucleus RNA sequencing (snRNA-seq) samples encompassing pathologically normal human nucleus accumbens, putamen, and caudate nucleus. We characterize 18 striatal neuron subtypes and validate their molecular signatures and spatial organization by *in situ* hybridization. Comparing to homologous mouse brain regions, we identify species differences along the dorsal-ventral axis, including in opioid receptor expression. In addition to the canonical segregation of MSNs into direct pathway MSNs expressing dopamine receptor 1 (D1) that project to the substantia nigra/internal globus pallidus, and indirect pathway MSNs expressing dopamine receptor 2 (D2) that project to the external globus pallidus, we characterize novel subtypes of D1 and D2 expressing MSNs with unique spatial arrangements and molecular profiles. By integrating our data with genome-wide association studies (GWAS) and *in vivo* mouse studies, we lay the foundation to define cell-type specific striatal dysfunction and implicate specific striatal neuron subpopulations in the etiology of substance use disorder and neuropsychiatric disease.