Name: Svitlana Bach
PI Name: Keri Martinowich
Email: svitlana.bach@libd.org
PI Email: Keri.Martinowich@libd.org

Molecular Profiling of the Human Nucleus Accumbens with Spatial and Single Nucleus Resolution

Svitlana Bach[1], Prashanthi Ravichandran[2], Nicholas J. Eagles[1], Madeline Valentine[1], Robert Phillips[1], Kelsey D. Montgomery[1], Thomas M. Hyde[1,4,5], Joel E. Kleinman[1,5], Stephanie C. Page[1], Leonardo Collado-Torres[1,3], Alexis Battle[2,6,7,8], Stephanie C. Hicks[2,3,8,9], Kristen R. Maynard[1,5,1], Keri Martinowich[1,5,10,11]

[1]Lieber Institute for Brain Development, Johns Hopkins Medical Campus, Baltimore, MD, USA; [2]Department of Biomedical Engineering, Johns Hopkins University School of Medicine (JHUSOM), Baltimore, MD, 21218, USA; [3]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [4]Department of Neurology, JHUSOM, Baltimore, MD, USA; [5]Department of Psychiatry and Behavioral Sciences, JHUSOM, Baltimore, MD, USA; [6]Department of Computer Science, Johns Hopkins University (JHU), Baltimore, MD, USA; [7]Department of Genetic Medicine, JHUSOM, Baltimore, MD, USA; [8]Malone Center for Engineering in Healthcare, JHU, Baltimore, MD, USA; [9]Center for Computational Biology, JHU, Baltimore, MD, 21205, USA; [10]The Solomon H. Snyder Department of Neuroscience, JHUSOM; [11]The Kavli Neuroscience Discovery Institute, JHU, Baltimore, MD, USA

The nucleus accumbens (NAc) is responsible for processing rewarding stimuli and reward-related learning. Addictive drugs elevate dopamine levels in the NAc, triggering epigenetic changes that alter gene expression to control drug-seeking behavior. Animal studies suggest that different subregions of the NAc differentially contribute to reward-related behaviors; however, they have not been comprehensively defined in the human NAc. We used the 10X Genomics single-nucleus 3' RNA sequencing (snRNA-seq) and Visium platforms to generate spatial transcriptomic maps of the human NAc. Analysis of snRNA-seq data identified 25 distinct cell types, including 16 neuronal and 9 non-neuronal populations. We identified four dopamine receptor D1 (DRD1) medium spiny neuron (MSN) subpopulations, two DRD2 MSN subpopulations, nine subpopulations of inhibitory neurons and a small cholinergic interneuron population. Two DRD1-expressing MSN subpopulations corresponded to D1+ islands based on marker gene expression DRD1, OPRM1, and RXFP1. Analysis of Visium data revealed several domains enriched in MSNs, including one expressing DRD1, OPRM1, and RXFP1, corresponding to the location of D1 islands. Additionally, we identified inhibitory neurons expressing SST and CORT throughout the NAc, spatial domains corresponding to white matter, and distinct pockets of astrocytes. Using non-negative matrix factorization and transfer learning, we plan to integrate these datasets to define gene expression patterns within the snRNA-seq data within the spatial transcriptomics landscape. Our study is the first to characterize spatial gene expression profiles of individual cell populations within the human NAc and provides a valuable resource for integrating transcriptomic data generated in animal drug addiction models.