Submitter Name: Svitlana V. Bach
Submitter Email: svitlana.bach@libd.org
PI Name: Keri Martinowich
PI Email: keri.matnowich@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, 11], Keri Martinowich[1, 5, 10, 11]

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

Located in the ventral striatum, the nucleus accumbens (NAc) receives dopaminergic projections from the ventral tegmental area, and 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 sub-regions of the NAc differentially contribute to reward-related behaviors; however, transcriptomic signatures for relevant cell types and spatial domains have not been comprehensively defined in the human NAc. We used the 10X Genomics Visium platform to generate a spatial transcriptomic map of the human NAc, which we coupled with single-nucleus RNA sequencing (snRNA-seq) with the 10X single cell 3' gene expression platform from adjacent tissue sections to spatially register molecularly-defined cell types. Fresh frozen postmortem brain tissue from adult neurotypical control donors (n=10) underwent stringent quality control to ensure high RNA integrity and accurate neuroanatomical localization. NAc tissue was scored and 10 µm thick sections were mounted onto Visium slides (2-5 capture areas per donor). We investigated molecularly-defined spatial domains, including areas comparable to the NAc shell and core sub-regions, as well as areas enriched in *OPRM1+/DRD1+* islands. Gene expression patterns were verified with orthogonal methods, including multiplex single molecule fluorescent in situ hybridization. Our study is the first to characterize spatial gene expression profiles of individual cell populations within the cytoarchitecture of the human NAc and provides a valuable resource for integrating transcriptomic data generated in animal models.