Name: Kristen R. Maynard Email: kristen.maynard@libd.org

Integrated single cell and spatial transcriptomic approaches for defining the molecular anatomy of reward circuitry in the human brain

Louise Huuki-Myers[1], Abby Spangler[1], Nick Eagles[1], Kelsey D. Montgomery[1], Sang Ho Kwon[1,2], Boyi Guo[3], Melissa Grant-Peters[4,5], Bukola Ajanaku[1], Erik Nelson[1], Josh Stolz[1], Heena R. Divecha[1], Madhavi Tippani[1], Chaichontat Sriworarat[1,2], Annie B. Nguyen[1], Prashanthi Ravichandran[6], Matthew N. Tran[1], Arta Seyedian[1], Svitlana Bach[1], Vijay Sadashivaiah[1], PsychENCODE consortium, Thomas M. Hyde[1,7,8], Joel E. Kleinman[1,7], Alexis Battle[6,9,10,11], Stephanie C. Page[1], Mina Ryten[4,5,12], Stephanie C. Hicks[3,11], Keri Martinowich[1,2,7], Leonardo Collado-Torres[1], Kristen R. Maynard[1,2,7]

[1]Lieber Institute for Brain Development, Johns Hopkins Medical Campus, Baltimore, MD, USA; [2]The Solomon H. Snyder Department of Neuroscience, Johns Hopkins School of Medicine (JHSOM), Baltimore, MD, USA; [3]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [4]Genetics and Genomic Medicine, Great Ormond Street Institute of Child Health, University College London, London, UK; [5]Aligning Science Across Parkinson's (ASAP) Collaborative Research Network, Chevy Chase, MD, USA; [6]Department of Biomedical Engineering, JHSOM, Baltimore, MD, USA; [7]Department of Psychiatry and Behavioral Sciences, JHSOM, Baltimore, MD, USA; [8]Department of Neurology, JHSOM, Baltimore, MD, USA; [9]Department of Computer Science, Johns Hopkins University (JHU), Baltimore, MD, USA; [10]Department of Genetic Medicine, JHSOM, Baltimore, MD, USA; [11]Malone Center for Engineering in Healthcare, JHU, Baltimore, MD, USA; [12]NIHR Great Ormond Street Hospital Biomedical Research Centre, University College London, London, UK

Given the close relationship between brain structure and function, assigning gene expression to distinct anatomical subdivisions and cell populations within reward structures of the human brain improves our understanding of these regions and how they contribute to neuropsychiatric disorders, including substance use disorders. To define the molecular architecture of key nodes of reward circuitry, we used the 10x Genomics Visium and single cell gene expression platforms to generate a data-driven spatial map of gene expression in the dorsolateral prefrontal cortex (DLPFC) of the adult human brain (n=10 neurotypical donors). Integration with paired single nucleus RNA-sequencing (snRNA-seq) data revealed distinct cell type compositions and cell-cell interactions across spatial domains. Using PsychENCODE and publicly available data, we mapped the enrichment of cell types and genes associated with neuropsychiatric disorders to discrete spatial domains. We also performed snRNA-seq in the human nucleus accumbens (NAc) and habenula (Hb) to generate a molecular atlas of cell types in these topographically-organized brain regions critical for reward processing. We present the first molecular profiles of distinct cell types in the human NAc and Hb to enhance translational studies of reward circuits in the human brain. By integrating these datasets with neuropsychiatric and substance use disorder gene sets, we provide novel insights into how genetic risk for psychiatric disorders maps to underlying brain structure and function.