

Submitter Name: Brion Maher
Submitted email: brion@jhhu.edu

An Examination of Differential Methylation and Gene Expression in Dorsolateral Prefrontal Cortex Following Opioid Overdose

David W. Sosnowski, Ph.D.¹, Andrew E. Jaffe, Ph.D.^{1,2}, Ran Tao, Ph.D.², Amy Deep-Soboslay, M.Ed.², Joel E. Kleinman, M.D., Ph.D.^{2,3}, Thomas M. Hyde, M.D. Ph.D.², Chang Shu, Ph.D.^{1,4}, Sarven Sabuncuyan, Ph.D.⁵, and Brion S. Maher, Ph.D.¹

¹ Department of Mental Health, Johns Hopkins Bloomberg School of Public Health

² Lieber Institute for Brain Development

³ Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine

⁴ Department of Pediatrics, Columbia University Irving Medical Center

⁵ Department of Pediatrics, Johns Hopkins University

Background: Opioid use continues to pose a significant risk to individuals throughout the globe, especially in the United States. Epigenetic changes have emerged as a leading potential biological marker of substance use given their implications for transcription regulation. We investigated methylation and gene expression differences in 160 post-mortem dorsolateral prefrontal cortex (dlPFC) samples, which consisted of 73 individuals who died of acute opioid intoxication, 59 group-matched psychiatric controls, and 28 group-matched normal controls. Methylation was measured using the Illumina Infinium MethylationEPIC BeadChip. Gene expression was measured via RNA-Seq. Thirteen CpGs surpassed a relaxed FDR significance threshold of .1. One of these sites was located within Netrin-1, a gene implicated in kappa opioid receptor activity. There also was modest association between opioid use and accelerated methylation PhenoAge. Sixteen genes were differentially expressed in opioid samples compared to control samples at an FDR threshold of .1. The top differentially expressed gene, NPAS4, was downregulated in opioid samples and has previously been implicated in cocaine use. While these results highlight potentially interesting genes and pathways, a limited overlap of these findings with existing studies points to the need for larger samples and combined analysis of existing samples.