Submitter Name: Julie White
Submitter Email: jdwhite@rti.org
PI Name: Dana Hancock
PI Email: dhancock@rti.org

Comparison of DNA methylation signals across substances reveals shared biological implications for substance use

Julie D. White[1], Kevin Liao[1], Psychiatric Genomics Consortium Substance Use Disorders Epigenetics Working Group, Dana B. Hancock[1]

[1]GenOmics and Translational Research Center, RTI International

A growing body of literature has highlighted many associations between epigenetic changes and substance use phenotypes. However, epigenetic changes shared across multiple substances are not well characterized. Though different substances largely interact with different neuroreceptors, all activate the brain's natural reward system, and recent genome-wide association studies have identified 100+ variants associated with multiple substance use phenotypes, indicating some shared genetic risk for addiction. Thus, we hypothesized that some epigenetic modifications would similarly be associated with several substance use phenotypes. To investigate this hypothesis, we focused on array-based DNA methylation in postmortem human brain and compared CpGs with differential methylation by cigarette smoking at death (N = 53 cases, 168 controls), acute opioid intoxication at death (N = 72 cases, 81 controls), lifetime cocaine use disorder (CUD; N = 21 cases, 21 controls), and lifetime alcohol use disorder (AUD; N = 61 cases, 58 controls). At a suggestive significance threshold of $p<1\times10^{-4}$, no CpGs overlapped across multiple substance phenotypes. However, there was overlap among the genes annotated to CpGs below this threshold: 11 genes shared between smoking and AUD, 4 genes shared between CUD and AUD, and no genes overlapping with opioid overdose results. In both sets, genes shared between substance use phenotypes had roles in signaling (e.g., *CAMKK1*, *TSPAN18*), cell adhesion (e.g., *CDH2*, *CDH23*, *MAGI1*), and transcription factor activity (e.g., *GATA4*, *ASCL4*). These overlapping genes may signify neurobiological mechanisms and gene functions implicated in several substance use disorders and important for advancing the understanding of addiction.