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# Brain Differential Methylation and Gene Expression following Opioid Overdose

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Opioid use continues to pose significant risk to individuals throughout the globe, especially in the United States. Epigenetic changes have emerged as a leading potential biological marker of drug dependence given their implications for transcription regulation and cellular reprogramming. 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 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, other than NPAS4, with existing studies points to the need for larger samples and combined analysis of existing samples.