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Deciphering the role of DNA hydroxymethylation in substance use disorders

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Substance use disorders (SUDs) are influenced by genetic and environmental factors. While recent research implicated epigenetic disturbances in SUDs, these studies have mostly focused on DNA methylation (5mC). DNA hydroxymethylation (5hmC) has been understudied in psychiatric disorders and addiction, despite being highly enriched in the brain where it regulates critical functions, including neural plasticity. Here, we conducted a parallel 5mC and 5hmC profiling of the orbitofrontal cortex (OFC) of SUDs, focusing on opioid use disorder (OUD) and alcohol use disorder (AUD). We integrate neuronal-specific 5mC and 5hmC as well as within-subject correlations with gene expression profiles from human postmortem samples. Further, co-methylation modules, genome-wide association studies (GWAS) enrichment, and drug repurposing analyses were conducted for 5mC and 5hmC in OUD and AUD. We identified hundreds to thousands of 5mC and 5hmC marks for both OUD and AUD, with enrichment for WNT signaling and neuronal processes, as well as GWAS of SUDs. Our findings replicate previous associations and identify novel loci epigenetically dysregulated in SUDs.

Further, we revealed 5hmC as an important regulatory mechanism in the human brain and suggest potential novel treatments for SUDs.