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Postmortem brain multi-omic profiling and vertical data integration in cocaine and opioid use disorder

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Substance use disorders (SUD) are a major public health problem with rising rates of overdoses and deaths. Therefore, understanding the neurotoxic effects of drugs of abuse is critical. Advances in genomic technologies, coupled with increased availability of postmortem brain tissue, have facilitated the generation of multi-level omics data, including epigenomics, transcriptomics, proteomics, in human brain. With this explosion of data comes a great need for vertical data integration and analyses across different molecular layers that allow cross-validation of network alterations.

We performed integration of RNAseq, microRNAseq, DNA methylation and proteomics in the dorsolateral prefrontal cortex (BA9) of subjects with cocaine (CUD) and opioid use disorder (OUD) compared to controls, accounting for covariates including age, sex, PMI, pH, and RNA integrity. Differential expression, co-expression, co-methylation, and/or pathway enrichment analyses identified localization to synapse and myelination pathways enriched in CUD, and acute inflammatory response and angiogenesis as the main enriched pathways in OUD. We found cell-type specific effects in these networks, and single nuclei RNAseq identified cell-type specific clusters that validate the findings obtained from whole tissue. Further, by integrating the miRNA biosignature's target genes with the Broad Institute Connectivity Map (CMap) we uncovered new druggable targets for repurposing of FDA approved drugs

Our results point to unique brain alterations induced by cocaine and opioids, suggesting distinct mechanisms of action and neurotoxicity. These results could shed light on the neurobiological mechanisms of SUDs and could lead to development of novel therapeutic approaches to minimize damage induced by these drugs of abuse.