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Epigenetics of Cocaine Use Disorder: A Collaborative Case-Control Initiative in Blood and Brain

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Recent studies have implicated a role for DNA methylation in modulating addictive behavior. In this study, we present preliminary data where we investigated blood methylome alterations in patients with cocaine use disorder (CUD, N=99) and controls (N=90) in a cohort from the region of Rio Grande do Sul, Brazil, as well as in blood and brain tissue (BA9) from 11 controls and 32 subjects with polysubstance use disorder, including cocaine, from the Houston area. Assessments were made using the Infinium MethylationEPIC BeadChip (Illumina) controlling for age, sex, BeadChip, batch, and blood cell type composition, adjusting for false discovery rate. In the Brazil cohort we identified significant differences in methylation of 34 genes. Of these, S100A8, a toll-like receptor 4 (TLR4), agonist was found by enrichment analyses to be involved in immune system pathways. In addition, we identified accelerated epigenetic aging in CUD subjects compared to controls, and this was correlated with severity of cocaine consumption. Accelerated epigenetic aging was also identified in BA9 of addiction subjects from the Houston cohort. Of interest, HYALP1 gene was nominally differentially methylated in both blood and brain from these subjects and brain methylation correlated with epigenetic aging in brain. HYALP1 degrades hyaluronan, an extracellular matrix protein that accumulates in the brain with aging. Hyaluronan accumulation in the brain may contribute to increased vulnerability to brain insults related to addiction. Our findings support a role of inflammation and extracellular matrix pathways in cocaine addiction, and may aid in future development of novel treatments for addiction.