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Demyelination and Accelerated Aging as Mechanisms of Cocaine-induced Neurotoxicity

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Chronic cocaine use causes changes in brain structure/function. However, few studies have addressed cocaine-induced neurotoxic consequences in human brain. Here we assessed blood epigenetic changes from 172 cocaine users (CUD) and 127 controls, and brain imaging (58 controls, 73 CUD) from the COCCAINE Brazilian cohort, and brain proteomic and epigenomic measures in BA9 of subjects who died of a cocaine overdose (N=10), and controls (n=12) from the UTHealth brain collection. Brain images were acquired on a 3T Signa GE scanner, and whole-brain fractional anisotropy (FA) maps were calculated from diffusion tension imaging (DTI) parameters. Voxelwise cross-subject statistics was performed between groups with age, sex, and head motion as covariates. Epigenetic assessments were made using the Infinium MethylationEPIC BeadChip, and DNA methylation age was estimated based on the Horvath algorithm. Proteomic analyses were performed using LC-MS/MS. We found reduced FA among CUD (FEW< .001) compatible with brain age effect on white matter, specially within females, and an inverse association between years of cocaine use and FA (R^2=0.15, p = .002). Further, accelerated epigenetic aging in blood from Brazilian CUD subjects correlated with severity of cocaine consumption. In brain we identified differential methylation across a 48-kb region spanning the *HOXA* gene cluster, implicated in aging. Proteomic analyses identified myelination pathways enriched in CUD subjects; specifically MOG, MAG, and LINGO-1 were decreased. Our results suggest demyelination and accelerated aging as a mechanism of cocaine-induced neurotoxicity. These results could lead to development of novel therapeutic approaches to minimize damage induced by cocaine abuse.