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Large-Scale Reorganization of DNA Methylation and Upregulation of Extracellular Matrix Genes in Cocaine Reward-Related Hippocampal Learning

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Cocaine addiction is characterized by compulsive drug use and relapse triggered by drug-related cues and contexts. The hippocampus encodes the spatial and contextual features of reward-associated learning. The dorsal dentate gyrus (dDG), by receiving contextual information from the entorhinal cortex and cocaine enhanced dopamine signals, is uniquely positioned to undergo substantial epigenetic and transcriptional changes to drive context-induced drug seeking and relapse. Here we report an unusually high number of methylation changes (~30,000) in the dDG following cocaine self-administration (SA) that is 10 times more than that produced by the purely environmental challenge of chronic unpredictable stress. These cocaine sensitive epigenetic regions were overrepresented in enhancers and associated with about half of the expressed genes (~8,000) of diverse gene ontology functions that, however, were not random and had relevance to neuronal plasticity. In contrast, only ~400 genes were upregulated in SA that included a significant number of differentially methylated genes. These genes were enriched in the organization of extracellular matrix (ECM), an extra-neuronal structure involved in neuronal connectivity and plasticity. The DNA methylation and gene expression structure of dDG suggests a poly/omni-epigenic model of context-driven cocaine seeking, similar to the proposed genetic architecture of omnigenic complex traits. This model involves interaction between a large number of epigenetically modified neuronal genes that have small effect size and a small group of differentially methylated and expressed core genes that have large effect size and direct connection to the neuroplasticity phenotype, driving hippocampal plasticity and acquisition of cocaine SA.