Epigenetic priming underlies transcriptional disruption linked to cocaine relapse

Philipp Mews¹, Hope Kronman¹, Aarthi Ramakrishnan¹, Molly Estill¹, Simone Sidoli², Benjamin Garcia², Li Shen¹, Eric J Nestler¹

¹Fishberg Dept. of Neuroscience, Icahn School of Medicine at Mount Sinai; ²Dept. of Biochemistry and Biophysics, Perelman School of Medicine University of Pennsylvania; ³Dept. of Biochemistry, Albert Einstein College of Medicine

Growing evidence implicates altered gene expression in mediating the lasting effects of cocaine, and more recent work supports a key role for epigenetic pathways in the molecular pathology of addiction. Permanent changes in chromatin structure are hypothesized to underlie the transcriptional disruption caused by cocaine, particularly in the nucleus accumbens (NAc), a key brain region of reward learning. However, the molecular mechanisms responsible remain unclear. The NAc is composed of two functionally distinct types of medium spiny neurons (MSNs), the D1 and D2 dopamine receptor-expressing subtypes, therefore making the cell-type specific identification of epigenetic changes critical. Here, we investigated the cocaine-induced changes in chromatin genome-wide by ATAC-seq in the distinct D1 and D2 MSN subtypes, and distinguished immediate versus persistent alterations in combination with unbiased histone modification profiling by mass spectrometry and ChIP-sequencing. We found that chronic cocaine persistently alters striatal chromatin structure, especially in D1 MSNs, involving eviction of the histone variant H2A.Z, a recently identified memory suppressor, at key neuronal genes. Curiously, genome accessibility in D1 MSNs is increased at these ‘scarred’ genes even after prolonged withdrawal, linked to dysregulated gene expression upon relapse. Together, our studies investigate an emerging view of epigenetic adaptation and gene dysfunction that may contribute to drug addiction, providing novel insight into epigenetic priming as an important mechanism whereby drugs of abuse alter brain function in lasting ways.