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Investigating the transcriptomic and epigenomic profile of the mouse striatum following cocaine exposure

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Recent evidence suggests that histone post-translational modifications (HPTMs) regulate neuronal gene expression by altering chromatin accessibility and transcription factor recruitment. Cocaine regulates gene expression, in part, via changes in HPTMs, many of which persist across abstinence. Bivalent gene promoters are simultaneously enriched in both activating (H3K4me3) and repressive (H3K27me3) HPTMs and become 'resolved' to either activation or repression by removal of either HPTM. We find nucleus accumbens activation of the immediate early gene, *Nr4a1*, immediately following mouse cocaine self-administration, which returns to baseline by 28 days of abstinence. However, the mechanism of this transient *Nr4a1* activation is unknown, and sex differences in *Nr4a1* activation by cocaine have yet to be interrogated. We hypothesized that *Nr4a1* gene regulation may be regulated by promoter HPTMs, specifically, changes in enrichment of repressive H3K27me3. To address this hypothesis, we applied the sequential chromatin-immunoprecipitation (ChIP) and qPCR to investigate the expression and epigenomic profile of three brain regions involved in the addiction pathway (striatum, prefrontal cortex, and hippocampus). Indeed, we found that cocaine exposure elicits a sex- and region-specific effect on *Nr4a1* activation, as well as a sex- and region-specific effect on Nr4a1 promoter bivalency. In the future, we will further probe the precise functional relevance of Nr4a1 bivalency using cell-type specific epigenetic editing in vivo.