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A Single Exposure to Cocaine Rewires the 3D Genome Structure of Midbrain Dopamine Neurons

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Midbrain dopamine neurons (DNs) respond to a first exposure to addictive drugs and play key roles in chronic drug usage. As the synaptic and transcriptional changes that follow an acute cocaine exposure are mostly resolved within a few days, the molecular changes that encode the long-term cellular memory of the exposure within DNs remain unknown. To investigate whether a single cocaine exposure induces long lasting changes in the 3D genome structure of DNs, we applied Genome Architecture Mapping and single nucleus transcriptomic analyses in the mouse midbrain. We found extensive rewiring of 3D genome architecture at 24 hours past acute cocaine exposure which remains or worsens by 14 days, outlasting transcriptional responses, which affects genes known to have major roles in cocaine-induced synaptic changes. Large genomic regions undergo structural changes in their compaction, including at post-synaptic and posttranscriptional regulatory genes. Polymer modeling revealed the progressive unfolding of Rbfox1, a regulator of alternative splicing, between 24 hours and 14 days past cocaine exposure, with increased structural variance at 14 days. Finally, detailed investigation of gene expression across DN subtypes showed that the genes that are structurally remodeled by cocaine are most expressed in a specific DN sub-type characterized by low expression of the dopamine autoreceptor Drd2, a key feature of cells highly sensitive to cocaine. These results reveal an important role for long-lasting 3D genome remodeling in the cellular memory of a single cocaine exposure, providing new hypotheses for understanding the inception of drug addiction and 3D genome plasticity.