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Single nucleus ATAC-seq of the central amygdala reveals patterns of chromatin accessibility associated with the cocaine self-administration rats

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The central amygdala (CeA) has been shown to play a critical role in cocaine craving, one of the primary drivers of relapse in individuals with cocaine use disorder. Our knowledge of the specific pathways and cell types involved in cocaine craving is still limited but new single cell technologies provide an opportunity to examine the effects of cocaine on individual cellular populations in the CeA. Here, we use single nucleus ATAC-seq (assay for transposase-accessible chromatin with sequencing) to characterize chromatin accessibility changes in the CeA of rats self-administering cocaine. A cohort of Sprague Dawley rats (n=6; 3 males, 3 females) was allowed to self-administer intravenous cocaine for ten consecutive days. Each cocaine-experienced rat was paired to a sex-matched, yoked saline control rat. 10x Genomics ATAC-seq libraries were generated from nuclei isolated from CeA punches. ATAC-seq data were analyzed with the R package Signac, resulting in identification of all expected glial and neuronal populations. Cell type-specific differentially accessible regions (DARs) were observed in cocaine-experience animals compared to the saline controls in both glia and neuronal subtypes, suggesting that cocaine-induced alterations in transcription in the CeA are mediated by chromatin conformation changes. Bioinformatic analyses identified upstream regulatory mechanisms and downstream signaling pathways associated with these cell type-specific DARs. These results indicate that repeated, daily cocaine self-administration is associated with distinct cell type-specific chromatin accessibility changes in the rat CeA. These findings highlight specific amygdalar cell populations and novel molecular substrates that could be targeted to reduce compulsive cocaine taking.