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Cellular and transcriptional contributions of the nucleus accumbens in transferring extinction-based memories

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Renewal of drug-seeking behaviors is often due to persistent memory retrieval of conditioned responses previously associated with drug contexts. While this becomes maladaptive as subjects fail to extinguish these behaviors, this correlates with faulty cellular, epigenetic, and transcriptional modifications in reward regions such as the nucleus accumbens (NAc) that facilitate relapse. Here, we used a rat model of contextual self-administration (SA; ABA), where rats acquire in context A, then extinguish in a different context (B), followed by a re-exposure test in context A (renewal). This is combined with RNA-sequencing (RNAseq) of NAc subregions (core/shell) to transcriptionally profile the impact of extinction learning on counteracting drug memories. Additional cell-type specific techniques such as fiber photometry and chemogenetics were used to characterize the contributions of D1 and D2 dopamine medium spiny neurons (MSNs) in the NAc. A heterogeneous distribution was observed in the ABA group, where two subgroups of rats showed extinction or renewal. Interestingly, these phenotypes were supported by differential transcriptional profiles in a subregion-dependent manner. In parallel, fiber photometry and chemogenetic analyses revealed cell-specific contributions of D1- or D2-MSNs. For instance, while D1-MSNs signal reward seeking and renewal, D2-MSNs seem to signal an anticipatory activity towards both processes. Consistent with this, chemogenetic inhibition of D1 or D2-MSNs in NAc-core decreased reward seeking during renewal, suggesting a key role of both cell types in the cocaine-associated renewal. Together, these approaches provide behavioral, cellular, and molecular evidence to develop novel venues to facilitate extinction transfer and prevent relapse.