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Capturing and profiling cocaine-recruited Arc neuronal ensembles encoding drug-context associations in the Nucleus Accumbens.

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Learned associations between the rewarding effects of drugs and the context in which they are experienced are decisive for precipitated drug-seeking and relapse in addiction. These associative memories are stored in sparse and highly discriminative populations of concomitantly activated neurons defining drug-recruited ensembles. In this study, we explore the dynamics and molecular mechanisms of both the recruitment of these ensembles upon initial drug exposure and their contribution to the encoding, strengthening and ultimately expression of drug-associated memories. Additionally, we explore the intrinsic and acquired cellular properties favoring the allocation of specific cells to these ensembles and/or predicting their further reactivation. Capitalizing on the activity-dependent labeling in Arc-CreERT2 mice (Denny et al., 2014), we captured and permanently tagged (fluorophores, channel-rhodopsin) cocaine-activated cells in the nucleus accumbens for further characterization, optogenetics, and nuclei sorting. We identified distinct subsets of neurons activated at both early and late stages of drug exposure and show that the reactivation of an initial ensemble correlates with behavioral sensitization. Similarly, re-exposure to a cocaine-paired context in a conditioned place preference (CPP) paradigm triggered cocaine ensembles' reactivation. Using optogenetics-mediated artificial reactivation, we found that populations recruited at early versus late stages of drug exposure had opposite roles in CPP expression. Single nucleus RNA Sequencing was then performed on FACS-isolated tagged neurons, and we successfully isolated a cluster of reactivated cells within the initially activated ensemble. Together, this ensemble-specific approach represents a pivotal step in identifying highly specific cellular processes involved in the encoding of pathological memories associated with addiction.