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In vivo labeling and molecular characterization of cocaine memory-specific active neurons using the photo-convertible calcium integrator CaMPARI2

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In abstinent drug users, cues previously associated with drug-taking can precipitate relapse long after the last instance of drug use. These maladaptive cue-drug associations are thought to be encoded in sparse patterns of strongly activated neurons (neuronal ensembles) typically identified using immediate early gene (IEG, e.g. Fos) expression. However, IEG-based approaches lack the temporal precision needed to label and characterize ensembles during short-lasting behavioral events (e.g, lever press / drug infusion). We employed a green-to-red photo-convertible calcium integrator, CaMPARI2, to permanently label cocaine-memory ensembles in infralimbic cortex (IL) of rats with sub-second temporal specificity during cocaine seeking.

Male and female Sprague-Dawley rats with CaMPARI2 virus and optical fibers in the infralimbic cortex were trained to self-administer cocaine (FR1, 0.75 mg/kg/infusion + light cue) during twice daily trial-based cocaine self-administration sessions (30 trials/ 3 h, 1 min lever-access/trial). Following training and 21 abstinence days, we used CaMPARI2-photoconversion to permanently label IL cocaine-memory ensembles during a 1 min cocaine-seeking test. We observed reliable cocaine self-administration during training and robust cue-induced cocaine seeking during the 1 min seeking test. CaMPARI2-snRNAseq revealed distinct clusters of glutamatergic and GABAergic IL neurons that subclustered into expected layer and subtypes. Further, IEGs were selectively induced in red ‘active’ neurons in the 10-min, but not 0-min group. We will identify unique DEGs within CaMPARI-labeled IL cocaine-memory ensembles and investigate DEG distribution across IL cell types. Molecular and cell-type characterization of drug-memory ensembles could help prevent relapse by selectively weakening persistent drug memories, without influencing other memories.