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Differential genetic expression within reward-specific ensembles in mice

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Maladaptive reward seeking is a hallmark of cocaine use disorder. To develop therapeutic targets, it is critical to understand the neurobiological changes specific to cocaine-seeking without altering the seeking of natural rewards, e.g., sucrose. The prefrontal cortex (PFC) and the nucleus accumbens core (NAcore) are known regions associated with cocaine- and sucrose-seeking ensembles, i.e., a sparse population of co-activated neurons. Within ensembles, transcriptomic alterations in the PFC and NAcore underlie the learning and persistence of cocaine- and sucrose-seeking behavior. However, transcriptomes exclusively driving cocaine seeking independent from sucrose seeking have not yet been defined using a within-subject approach. Using Ai14:cFos-TRAP2 transgenic mice in a dual cocaine and sucrose self-administration model, we fluorescently sorted (FACS) and characterized (RNAseq) the transcriptomes defining cocaine- and sucrose-seeking ensembles. We found reward- and region-specific transcriptomic changes that will help develop clinically relevant genetic approaches to decrease cocaine-seeking behavior without altering non-drug reward-based positive reinforcement.