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Identifying reward-specific transcriptomes underlying polyreward seeking ensembles in the nucleus accumbens core and prelimbic cortex

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Substance use disorder (SUD) causes chronic drug-seeking in millions of humans across the globe and is yet to have dynamic and effective pharmacological treatments. This is partly due to the lack of understanding of reward-specific mechanisms underpinning and driving drug-seeking behavior apart from other biologically necessary reward-seeking behaviors e.g., eating. Adjacently, there has been a rise in polysubstance use i.e., using both opioids (heroin and fentanyl) and stimulants (cocaine), which has added to the complexity of creating effective treatments to reduce drug-seeking. Formation and maintenance of discrete neuronal networks, or ensembles, have been shown to underly goal-directed drug-seeking that is partially shared with other biological rewards such as sucrose intake. We know from previous research that genetic factors regulate cocaine-, opioid- and sucrose-seeking behavior. However, which factors regulating seeking behavior for each specific reward is not well understood. We aimed to define and differentiate reward-specific genetic signatures underlying drug-seeking using self-administration behavioral models for cocaine/sucrose, cocaine/fentanyl, and cocaine/heroin polyreward operant conditioning. We utilized TRAP2 transgenic mice in parallel with fluorescently activated cell sorting to perform sex-specific bulk and single-cell RNA sequencing for genetic characterization cFos-dependent reward-specific ensembles in regions associated with reward-seeking behavior e.g., the nucleus accumbens core and prelimbic cortex. We find that there are discrete region-specific genetic signatures that are exclusive to each reward-specific seeking behavior. Our investigations expand our genetic understanding of SUD in a clinically relevant model of polysubstance-seeking and will contribute to the treatment and prevention of SUD.