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HOT TOPICS

Single-cell transcriptional profiling in brain reward structures

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Brain reward circuits are frequently disrupted in neuropsychiatric and substance use disorders. For example, substance use disorders are associated with prolonged molecular changes in reward-related regions including the ventral tegmental area (VTA), nucleus accumbens (NAc), prefrontal cortex, hippocampus, and amygdala. However, cellular heterogeneity has impeded progress in understanding the molecular mechanisms contributing to disease. While previous studies identified unique functions for cell types in these regions, they lacked comprehensive information on transcriptional diversity.

To overcome these challenges, recent studies used single-cell and single-nucleus RNA-sequencing (sc/snRNA-seq) approaches to generate molecular profiles of cell types in reward-related regions of the rodent, non-human primate, and human brain [1–6]. These data enabled the identification of cell types that (1) are activated by exposure to motivational cues, including psychoactive drugs; (2) harbor enrichment for genetic risk associated with substance use and neuropsychiatric disorders; and (3) converge/diverge across species. Such analyses can identify and prioritize targets at the level of specific genes and gene programs within cell populations that contribute to the reward function.

For example, while roles for VTA dopamine neurons are well studied, GABAergic and glutamatergic neurons in the VTA also contribute to reward signaling, and parallel lines of evidence suggest that some VTA neurons may synthesize and release multiple neurotransmitters. Using snRNA-seq we confirmed the identity of combinatorial neurons in rat VTA, and elucidated novel marker genes for these populations [5]. Moreover, we demonstrated cell-type-specific enrichment for gene sets associated with risk for brain disorders and phenotypes related to substance use [5]. Similarly, to understand cell-specific responses to drugs with addictive potential that alter dopamine concentrations in the NAc, we generated a molecular atlas of the rat NAc at single-cell resolution following cocaine experience. Dopaminoceptive medium spiny neurons (MSNs), the principal NAc cell type, are functionally segregated into D1 and D2 receptor-expressing subtypes. Cocaine elevated activity-regulated gene expression selectively in D1-MSNs, an effect that was driven by a relatively small cluster of neurons [1]. In contrast, another scRNA-seq study examining morphine response in mouse NAc identified robust transcriptional activation of glia, highlighting the utility of these approaches in identifying substance-specific molecular changes [6].

Interpreting clinical relevance and extending findings from animal models to treatments requires understanding how cell types that contribute to the reward function differ across species. Toward this goal, we used snRNA-seq to generate a molecular taxonomy of cells across key nodes of the human brain reward circuitry (NAc, prefrontal cortex, hippocampus, and amygdala) [2]. In NAc, we identified discrete subpopulations of D1 and D2-MSNs to which we mapped cell-type-specific enrichment for genetic risk associated with both psychiatric disease and substance use. While many cell populations in the NAc were conserved, we also identified transcriptional differences in MSN subpopulations between rats and humans, indicating the presence of unique molecular features in analogous populations, or the existence of species-specific subclasses [2]. Together, these results advance our understanding of molecular mechanisms of neuropsychiatric disease and substance use disorders by revealing not only which individual cell ensembles contribute to reward processing, but also how genetic variation may influence these effects in the human brain.

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AUTHOR CONTRIBUTIONS

JJD and KM contributed equally to the conceptualization and writing of this manuscript. Both authors approved the final version of the paper.

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COMPETING INTERESTS

KM is the Social Media Editor for *Neuropsychopharmacology*.

ADDITIONAL INFORMATION

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