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A complex gene program initiates brain changes in response to cocaine

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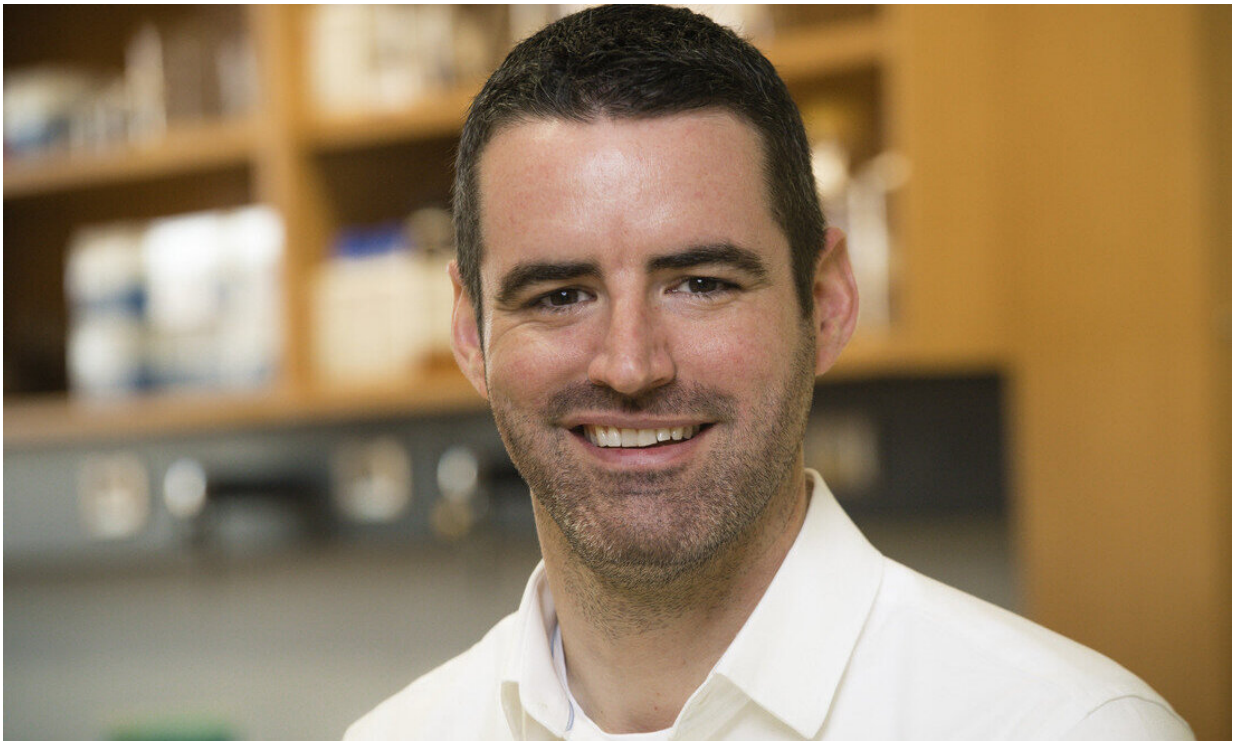

Jeremy Day. Credit: UAB

The lab of Jeremy Day, Ph.D., at the University of Alabama at Birmingham, has used single-nucleus RNA sequencing approaches to compare transcriptional responses to acute cocaine in 16 unique cell populations from a portion of the brain called the nucleus accumbens, or NAc. This molecular atlas is "a previously unachieved level of cellular

resolution for cocaine-mediated gene regulation in this region," said Day, an associate professor in the UAB Department of Neurobiology.

The atlas was just the beginning of a major study, published in the journal *Science Advances*, that used multiple cutting-edge technologies to describe a dopamine-induced gene expression signature that regulates the brain's response to cocaine.

"These results mark a substantial advance in our understanding of the neurobiological processes that control drug-related adaptations," Day said. "They also reveal new information about how transcriptional mechanisms regulate activity-dependent processes within the central nervous system."

The approaches used in this study, Day says, may also help dissect the role of similar gene programs that mediate other types of behavior, memory formation or neuropsychiatric disorders.

The NAc is deeply involved in drug addiction, and detailed understanding of how drugs alter its neural circuitry to initiate addictive behavior can suggest new therapeutic interventions. The NAc is a central integrator of the brain's reward circuit, and all addictive drugs acutely raise the level of the neurotransmitter dopamine in the NAc. Dopamine signaling during repeated drug use leads to widespread changes in gene expression, initiating alterations in neural synaptic circuitry and changes in behavior associated with drug addiction.

Previous studies of changes in NAc gene expression were only able to look at bulk tissue—a mix of many different cell types. When the Day lab looked at single cell changes by RNA-sequencing 15,631 individual rat NAc nuclei, they found a surprise. Only a small fraction of neurons in the NAc were transcriptionally responsive to cocaine administration—mainly a specific subcluster of medium spiny neurons

that express the Drd1 dopamine receptor.

The researchers next comprehensively defined the core gene structure that is activated when dopamine is added to a striatal neuron culture system. Similar to the responses in the rat NAc after cocaine administration, transcriptional activation predominantly occurred in Drd1-receptor-medium spiny neurons. Day and colleagues identified a core set of around 100 genes altered by dopamine, which also correlated with key genes activated in the NAc of rats given cocaine.

It has been hypothesized that gene expression programs in the brain work in concert to produce downstream effects on neuronal function and behavior. However, until recently researchers have lacked a way to test key gene expression programs, which requires inducing multiple genes at the same time.

Day and colleagues engineered a multiplexed CRISPR guide-RNA array to target 16 of the top candidate genes altered by dopamine. When paired with a neuron-optimized CRISPR/dead-Cas9 activation system, they were able to simultaneously upregulate the 16 genes in neuronal cultures or in the NAc of live rats. They then explored the transcriptional, physiological and behavioral consequences.

In primary neuronal culture, induction of this gene signature produced large-scale transcriptional changes that were enriched for genes involved in synaptic plasticity, neuronal morphogenesis and ion channel function. This program also significantly increased neuron burst firing frequency. In live rats, induction of the gene signature produced sensitization to repeated cocaine administration. These changes seen in the neuronal culture and live rats are similar to the neuronal and behavioral changes initiated by drugs of abuse.

Day says his group's study is the first proof-of-principle evidence that

CRISPR activation can be used for simultaneous and selective regulation of a gene expression signature in vivo.

"Critically," Day said, "these results represent the first demonstration—to our knowledge—of multiplexed gene regulation in any neuropsychiatric model, providing a roadmap for future studies to investigate the relationship between altered gene programs and neuronal disease states.

"While the present work provides insight into how cellular diversity contributes to transcriptional responses after an initial cocaine experience," Day said, "repeated exposure to drugs of abuse promotes neurophysiological adaptations that are thought to drive compulsive drug-seeking long after cessation of use. Hence, it will be critical for future studies to expand on this work by examining the transcriptional consequence of repeated or self-administered drug use at the single-cell level, as well as understanding how these changes are maintained within different cell populations over longer periods of time and as a result of volitional drug experience."

More information: Katherine E. Savell et al, A dopamine-induced gene expression signature regulates neuronal function and cocaine response, *Science Advances* (2020). DOI: 10.1126/sciadv.aba4221

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