Substance use linked to long-lasting brain changes, cognitive decline

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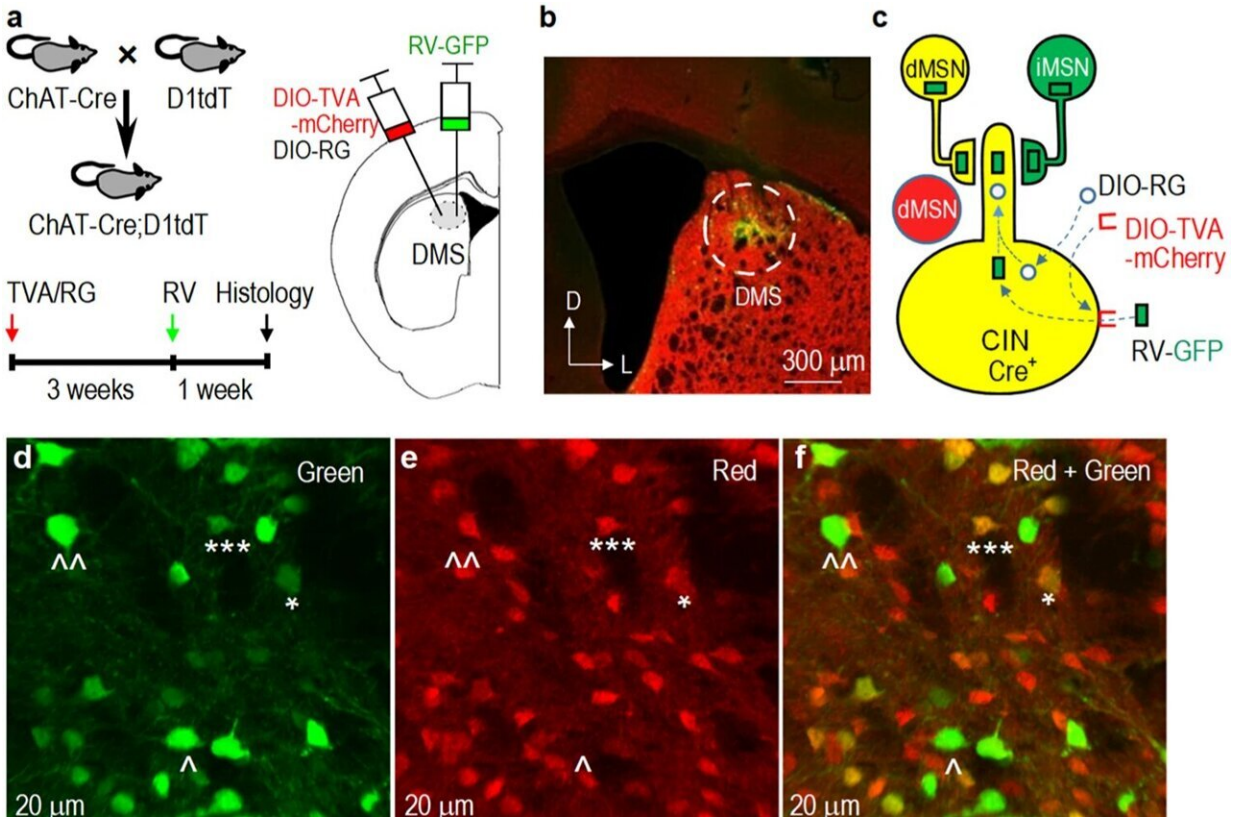

CINs receive striatal inputs primarily from dMSNs. **a** Schematic of experimental design. Cre-dependent helper viruses (AAV-DIO-TVA (EnvA receptor)-mCherry and AAV-DIO-RG (rabies glycoprotein)) were infused into the dorsomedial striatum (DMS) of ChAT-Cre;D1-tdTomato (tdT) mice, followed by rabies virus (RV-GFP) infusion at the same site 3 weeks later. Coronal sections were prepared 1 week after rabies virus infusion and were stained for choline acetyltransferase (ChAT; far-red, pseudo colored with cyan). **b** Confocal micrograph showing the injection site and viral expression in the

DMS. L lateral, D dorsal. **c** Schematic showing viral expression and retrograde spread of RV-GFP. AAV-DIO-TVA-mCherry and AAV-DIO-RG infected Cre-positive cholinergic interneurons (CINs). RV-GFP infected TVA-positive CINs (starter cells expressed GFP and mCherry), labeling their presynaptic neurons with GFP. Since direct-pathway medium spiny neurons (dMSNs) were labeled red (from D1-tdT), dMSNs presynaptic to the starter CINs were yellow (red and green overlap), whereas putative indirect pathway MSNs (iMSNs) were green. **d–h** Confocal micrographs of a DMS section; *Starter CINs, ***dMSN→CIN, ^^iMSN→CIN, ^CIN→CIN. **i** Summarized data showing that significantly more dMSNs (yellow) than iMSNs (green only) project to CINs; *$p = 0.036$. **j** AAVretro-DIO-ChR2-eGFP (Channelrhodopsin-2) was infused into the substantia nigra pars reticulata (SNr) of D1-Cre;ChAT-eGFP mice and DMS CINs were recorded. **k** Image of the DMS demonstrating ChR2-eGFP expression in dMSNs (cell membrane) and eGFP expression in CINs (cytoplasm). **l** Summarized optically-induced inhibitory postsynaptic currents (oIPSCs) recorded from CINs. **m** A burst of light stimulation (470 nm, 20 Hz, 5 pulses) of SNr-projecting dMSNs inhibited CIN firing. Unpaired *t* test (**i**). $n = 4$ mice (**i**) and 8/3 (**l**). Data are presented as mean values ± SEM. Source data are provided as a Source Data file. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-39623-x

An estimated 50 million individuals in the United States struggle with the challenges of cocaine or alcohol use disorders, according to the National Institutes of Health (NIH). Beyond the well-documented health risks, addiction to these substances detrimentally affects our cognitive flexibility, which is the ability to adapt and switch between different tasks or strategies. Although previous research has hinted at this connection, the underlying reasons for this cognitive impairment remain elusive.

Cognitive flexibility is a crucial element in various domains of our life, including academic achievement, employment success and transitioning into adulthood. As we age, this flexibility plays an important role in

mitigating cognitive decline. A deficiency in cognitive flexibility, however, is linked to academic deficits and a lower quality of life.

A study led by Dr. Jun Wang, associate professor in the Department of Neuroscience and Experimental Therapeutics at the Texas A&M University School of Medicine, provides new insight into the damaging impact that chronic cocaine or alcohol use has on cognitive flexibility.

The research, published in the journal of *Nature Communications*, emphasizes the role of the local inhibitory brain circuit in mediating the negative effects of substance use on cognitive flexibility.

Substance use influences a specific group of neurons called striatal direct-pathway medium spiny neurons (dMSNs), with projections to a part of the brain known as the substantia nigra pars reticulata (SNr). Conversely, cognitive flexibility is facilitated by striatal cholinergic interneurons (CINs), which receive potent inhibitory signals from the striatum.

"Our hypothesis was that increased dMSN activity from substance use inhibits CINs, leading to a reduction in cognitive flexibility," Wang said.

"Our research confirms that substance use induces long-lasting changes in the inhibitory communication between dMSNs and CINs, consequently dampening cognitive flexibility. Furthermore, the dMSN-to-SNr brain circuit reinforces drug and alcohol use, while the associated collateral dMSN-to-CIN pathway hinders cognitive flexibility. Thus, our study provides new insights into the brain circuitry involved in the impairment of cognitive flexibility due to substance use."

More information: Himanshu Gangal et al, Drug reinforcement impairs cognitive flexibility by inhibiting striatal cholinergic neurons, *Nature Communications* (2023). DOI: 10.1038/s41467-023-39623-x

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