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Dopamine-induced change in transmitter phenotype is a shared mechanism for drug-induced generation of cognitive deficit

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Drugs of abuse can affect the functioning of the medial prefrontal cortex (mPFC) and induce long-lasting cognitive deficits. However, it is unclear whether different drugs generate cognitive deficits through the same mechanism.
Here we analyzed the effects of phencyclidine (PCP) and methamphetamine (METH), two drugs of abuse that differ in their acute effects and pharmacology but cause similar long-lasting cognitive impairments. Repeated exposure to either drug induced approximately 600 glutamatergic neurons in the mPFC to start expressing GABA. Preventing this gain of GABA expression prevented drug-induced cognitive deficits, indicating a link between this change in transmitter phenotype and behavioral impairment.
Using a tamoxifen-inducible system, we showed that PCP and METH alter the transmitter identity of the same mPFC neurons, prompting an investigation into the underlying mechanism of drug action. Both PCP and METH acutely promote the phasic firing of dopaminergic neurons in the ventral tegmental area (VTA), increasing dopamine levels in the mesocorticolimbic system. Chemogenetically suppressing the activity of VTA dopaminergic neurons during treatment with PCP or METH prevented mPFC glutamatergic neurons from gaining GABA. Furthermore, optogenetically inducing phasic firing of VTA dopaminergic neurons in the absence of drug treatment every day for ten days was sufficient to cause mPFC glutamatergic neurons to gain GABA, raising the possibility that other drugs of abuse elicit a similar effect by increasing dopamine signaling.
The results reveal that a switch in the transmitter identity of mPFC neurons is a shared mechanism by which exposure to different drugs can generate cognitive deficits.