Human cocaine and heroin addiction tied to impairments in specific brain circuit initially implicated in animals

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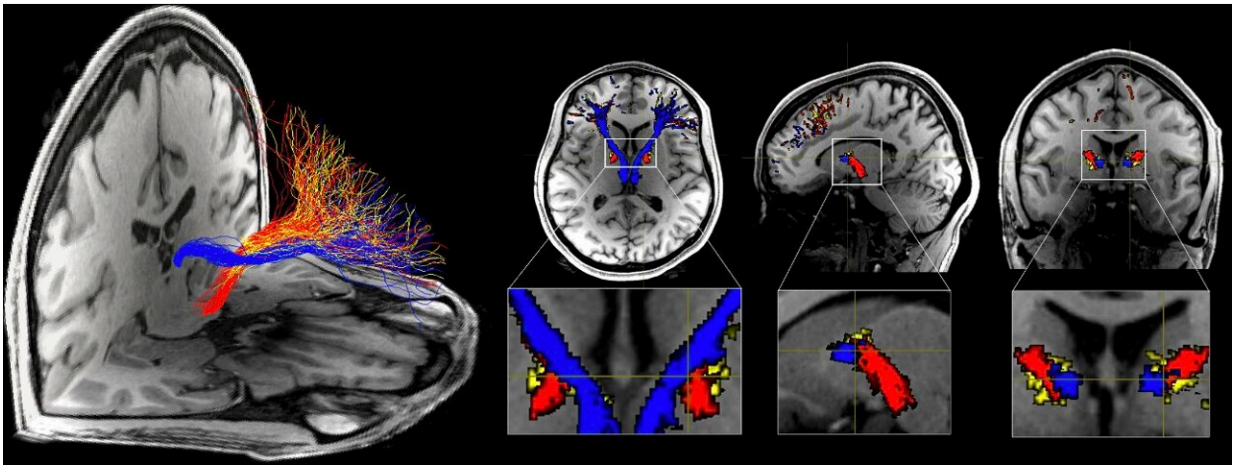

Structural connections with the prefrontal cortex modeled from targeted nuclei in the subcortex (blue: habenula, yellow: anterior thalamus, red: ventral tegmental area) using diffusion MRI tractography. Microstructural properties of the habenula tract were uniquely reduced in individuals with cocaine or heroin use disorder. Results highlight the potential specificity of distinct prefrontal cortical connections to the neuropathology of drug addiction. Credit: Mount Sinai Health System

White matter in the brain that was previously implicated in animal studies has now been suggested to be specifically impaired in the brains of people with addiction to cocaine or heroin, according to a study

conducted by researchers from the Icahn School of Medicine at Mount Sinai and Baylor College of Medicine. The study was published October 6 in *Neuron*.

The study looked at the connectivity of the tract between the prefrontal cortex (PFC), a brain region critical for regulating higher-order executive functions, and the habenula, a region that plays a critical role in reward and reward-associated learning. The habenula has emerged as a key driver of drug-seeking behaviors in animal models of addiction.

Specifically, signaling from the PFC to the habenula is disrupted in rodent cocaine addiction models, implicating this PFC-habenula circuit in withdrawal and cue-induced relapse behaviors. However, until now, the PFC-habenula path has remained poorly understood in the human brain. Furthermore, its involvement in the neuropathological effects of drugs other than cocaine has not been previously explored.

For the first time in the human brain, a team led by Rita Z. Goldstein, Ph.D., and Junqian Xu, Ph.D., used diffusion magnetic resonance imaging (MRI) tractography to investigate the microstructural features of the PFC-habenula circuit in people with cocaine or heroin addiction compared to healthy control participants. Diffusion MRI tractography uses noninvasive brain imaging to model fiber bundles in the living human brain.

Dr. Goldstein is the Mount Sinai Professor in Neuroimaging of Addiction and Director of the Neuroimaging of Addictions and Related Conditions Research Program at Icahn Mount Sinai. Dr. Xu is Associate Professor of Radiology, and Psychiatry, at Baylor College of Medicine.

"In addition to identifying microstructural differences, specifically reduced coherence in the orientation of the white matter fibers in the cocaine-addicted group that comprised both current cocaine users and

those with short-term abstinence, we extended results beyond cocaine (a stimulant) to heroin (an opioid), suggesting that abnormalities in this path may be generalized in addiction," said Sarah King, a Ph.D. student in Neuroscience in the Graduate School of Biomedical Sciences at Icahn Mount Sinai, who led the analyses and is first author of the paper.

"Importantly, we found that across all addicted individuals, greater impairment was correlated with earlier age of first drug use, which points to a potential role for this circuit in developmental or premorbid risk factors."

The results advance ongoing research in the field by targeting a previously unexplored circuit in the pathophysiology of addiction in humans, where deficits may predispose an individual to both the development of drug addiction and to relapse and which may be potentially amenable for individually tailored treatment or prevention efforts.

More information: Rita Z. Goldstein, Prefrontal-Habenular Microstructural Impairments in Human Cocaine and Heroin Addiction, *Neuron* (2022). DOI: 10.1016/j.neuron.2022.09.011. www.cell.com/neuron/fulltext/S0896-6273(22)00816-9

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