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Early exposure to cannabis boosts young brains' sensitivity to cocaine, rodent study finds

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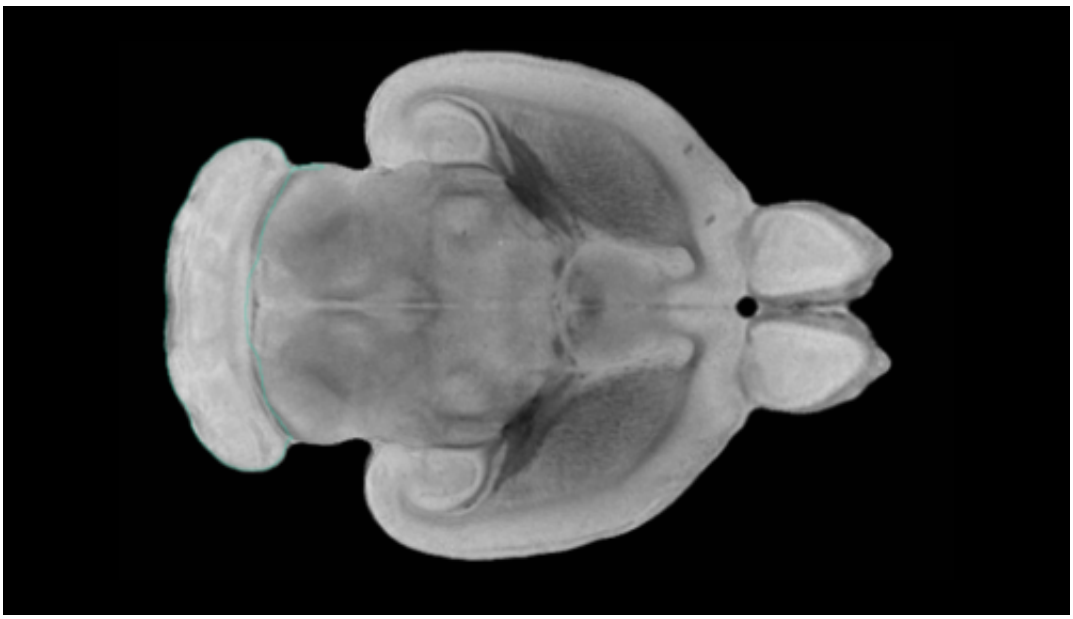

Cerebellum of CIVM postnatal rat brain atlas. Credit: Neurolex

Cannabis use makes young brains more sensitive to the first exposure to cocaine, according to a new study on rodents led by scientists at Columbia University and the University of Cagliari in Italy. By monitoring the brains of both adolescent and adult rats after giving them synthetic psychoactive cannabinoids followed by cocaine, the research team identified key molecular and epigenetic changes that occurred in the brains of adolescents—but not adults. This discovery reveals a new

interplay between the two drugs that had never previously been directly observed in biological detail.

These findings, reported this week in the *Proceedings of the National Academy of Sciences*, provide new understanding of how the abuse of cannabis during teenage years may enhance the first experience with cocaine and lead to continued use among vulnerable individuals.

"We know from human epidemiological studies that individuals who abuse cocaine have a history of early cannabis use, and that a person's initial response to a drug can have a large impact on whether they continue to use it. But many questions remain on how early cannabis exposure affects the brain," said epidemiologist Denise Kandel, Ph.D., who is a professor of Sociomedical Sciences in Psychiatry at Columbia's Vagelos College of Physicians and Surgeons and co-senior author of today's paper.

"Our study in rats is the first to map the detailed molecular and epigenetic mechanisms by which cocaine interacts with brains already exposed to cannabinoids, providing much-needed clarity to the biological mechanisms that may increase the risk for drug abuse and addiction," added co-author and Nobel laureate Eric Kandel, MD, codirector of Columbia's Mortimer B. Zuckerman Mind Brain Behavior Institute and Senior Investigator of the Howard Hughes Medical Institute.

Previous research had revealed key differences in how cannabis and cocaine affect brain chemistry. "Studies on the addictive properties of cocaine have traditionally focused on the mesolimbic dopaminergic pathway, a brain system that underlies our motivation to pursue pleasurable experiences," said Philippe Melas, Ph.D., who was an associate research scientist in Eric Kandel's lab at Columbia's Zuckerman Institute and is the paper's co-senior author. "While cannabis enhances mesolimbic dopaminergic activity similarly to cocaine, it also

affects an entirely different neurochemical system that is widespread in the brain called the endocannabinoid system. This system is essential for brain development—a process that is still ongoing in adolescence."

Besides the dopaminergic system, both cannabis and cocaine appear to share some additional features. Recent studies have suggested that the development of cocaine craving is dependent on the brain's glutamatergic system. This system uses glutamate, a brain molecule that acts as a synaptic transmitter in the brain, enhancing the transmission of signals between the brain's neurons. According to previous research, as well as findings presented in today's new study, using cannabis during adolescence may also affect this glutamatergic signaling process.

To delve deeper into a potential link between the two drugs, Dr. Melas and the husband-and-wife team of Drs. Eric and Denise Kandel partnered with Paola Fadda, Ph.D., Maria Scherma, Ph.D., and Walter Fratta, Ph.D., researchers in the Department of Biomedical Sciences, at the University of Cagliari in Italy. The group examined the behavioral, molecular and epigenetic changes that occur when both adolescent and adult rats are first exposed to WIN, a synthetic cannabinoid with psychoactive properties similar to those of THC found in cannabis, and then are subsequently exposed to cocaine.

"We found that adolescent rats that had been pre-exposed to WIN had an enhanced reaction to their initial exposure to cocaine. Notably, we observed this effect in adolescent but not in adult rats," said Dr. Melas, who is now a junior researcher in the Department of Clinical Neuroscience at the Karolinska Institutet in Sweden.

Upon further examination, the team found that, when preceded by a history of psychoactive cannabinoid use in adolescence, exposure to cocaine sets off a battery of unique molecular reactions in the rat brain. These reactions included not only changes in the aforementioned

glutamate receptors but also key epigenetic modifications. Epigenetic modifications are distinct, in that they affect the way genes are switched on or off but do not affect the sequence of the genes themselves.

The Columbia team had previously found similar epigenetic mechanisms in adult animals in response to nicotine and alcohol in the brain's reward center, known as the nucleus accumbens. In the present study, however, the epigenetic effects of cannabinoids were found to be specific to adolescents and to target the brain's prefrontal cortex. The prefrontal cortex, which plays a role in various executive functions, including long-term planning and self-control, is one of the last regions of the brain to reach maturity, a fact that has long been linked to adolescents' propensity for risky behavior.

Moreover, aberrant prefrontal cortex activity is often observed in patients suffering from addiction. Efforts to enhance the function of the prefrontal cortex are currently being evaluated in the treatment of addiction through the use of brain stimulation and other methodologies.

"Our findings suggest that exposure to psychoactive cannabinoids during adolescence primes the animals' prefrontal cortex, so that it responds differently to cocaine compared to animals who had been given cocaine without having previously experienced cannabis," said Dr. Melas.

These results in rats offer important clues to the biological mechanisms that may underlie the way that different classes of drugs can reinforce each other in humans. The results also support the notion that cannabis abuse during adolescence can enhance a person's initial positive experience with a different drug, such as cocaine, which in turn can have an effect on whether that person chooses to continue, or expand, their initial use of cocaine.

"This study suggests that teenagers who use cannabis may have a

favorable initial reaction to cocaine, which will increase their likelihood of engaging in its repeated use so that they eventually become addicted, especially if they carry additional environmental or genetic vulnerabilities," said Dr. Denise Kandel.

Most research involving rodents and addiction has traditionally focused on adult animals. It has also largely been limited to studying one substance of abuse at a time, without taking into consideration a history of drug exposure in adolescence.

"These and other experiments are key to understanding the molecular changes to the brain that occur during drug use," said Dr. Eric Kandel, who is also University Professor and Kavli Professor of Brain Science at Columbia. "This knowledge will be crucial for developing effective treatments that curb addiction by targeting the disease's underlying mechanisms."

This paper is titled "Cannabinoid exposure in rat adolescence reprograms the initial behavioral, molecular and epigenetic response to cocaine."

More information: Maria Scherma el al., "Cannabinoid exposure in rat adolescence reprograms the initial behavioral, molecular, and epigenetic response to cocaine," *PNAS* (2020). www.pnas.org/cgi/doi/10.1073/pnas.1920866117

Provided by Columbia University

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