A boost in dopamine during adolescence permanently amplifies dopamine function, impulsivity, and aggression in mice

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In a breakthrough finding researchers at Columbia University Irving Medical Center identified a sensitive developmental period during

adolescence that impacts adult impulsivity, aggression, and dopamine function in mice.

As organisms grow from embryo to adult, they pass through sensitive time-periods where developmental trajectories are influenced by environmental factors. These windows of plasticity often allow organisms to adapt to their surroundings through evolutionarily selected mechanisms.

The new findings, published online today in the journal *Molecular Psychiatry,* indicate that stimulant drug exposure highjacks this period with potentially harmful consequences to healthy kids but also beneficial ones to kids with pathological dopamine hypofunction.

The dopamine system is pivotal in modulating and shaping adolescent behaviors. Dopamine system dysfunction is commonly implicated in adolescent-onset neuropsychiatric disorders, such as attention deficit disorders, depression disorders, and schizophrenia.

"First, we found that dopamine transporter blockade in mice during their mid-adolescence from postnatal day 32 to 41, but not before or after, increases adult aggression, impulsivity and the behavioral response to amphetamine in mice. We then found that dopaminergic neurons are also more active in these animals," said Darshini Mahadevia, Ph.D., a research scientist at Columbia University Irving Medical Center (CUIMC), who co-led the study along with Deepika Suri, Ph.D. and Giulia Zanni, Ph.D., also research scientists at CUIMC.

To test for a causal relationship between altered neuronal activities and behavior, the researchers next applied modern genetic tools to artificially stimulate dopaminergic neurons during behavioral tasks that measure impulsivity.

In one such task, mice are trained to press a lever to receive a reward. Once mice become proficient at the task, they have to learn a new rule—withholding from pressing the lever to get rewarded. Mice that had their dopamine transporters blocked during mid-adolescence and mice that have their dopamine neurons artificially stimulated both perform badly on withholding from lever-pressing for rewards.

In another impulsivity task, mice are given the choice between a small immediate reward and a large later reward, the mouse version of the marshmallow test in humans, both assessing delay discounting. "Again, the pharmacologic as well as the direct neuronal manipulation both increase impulsive behavior, making mice choose the immediate small rewards over the large later rewards," said Dr. Suri.

While the investigation of sensitive periods in brain development has a long history, it has largely been focused on sensory systems. As an early recognition for the significance of this fundamental process, Hubel and Wiesel received the Nobel Prize in Physiology and Medicine (1981) for their work on ocular dominance plasticity in the 1960s.

"Studying sensitive developmental periods that impact complex behaviors, such as impulsivity and aggression, is novel and will aid in understanding the origins of psychiatric disorders, as well as their diagnosis, prevention, and treatment," said Dr. Zanni.

"By identifying these 'negative' consequences of adolescent dopamine transporter blockade on brain development and behavior in mice, we are tempted to speculate that adolescent stimulant exposure in humans will likewise increase aggression, impulsivity, and potential susceptibility to drug addiction later in life."

The researchers said that because the experiments were performed in wild-type animals, the findings cannot directly translate to the clinically

appropriate use of psychostimulants (for example to treat attention deficit disorders), but perhaps more so to chronic recreational use or improper prescription.

In a diseased state that results from dopamine system hypofunction, transient exposure to psychostimulants during adolescence might potentially be corrective, but this hypothesis needs to be experimentally tested.

"Critically, we argue that an understanding of the underlying biology is necessary for a clear risk/benefit evaluation of recreational or therapeutic drug exposure prior to adulthood" said Dr. Ansorge, the senior author of the study.

More information: Deepika Suri et al, Dopamine transporter blockade during adolescence increases adult dopamine function, impulsivity, and aggression, *Molecular Psychiatry* (2023). DOI: 10.1038/s41380-023-02194-w

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