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Enduring Effects of Adolescent Drug Exposure

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Adolescence is a risky time. Teenagers take risks and seek novelty by nature, and those actions affect their health. They are more likely to die from accidents, and experimentation with psychoactive drugs is normative. A persuasive body of literature shows that substance-using adolescents are far more likely to become drug-dependent adults than those who delay experimentation until young adulthood. Moreover, there is a direct correlation between the age of initiation for alcohol or tobacco use and adult dependence on these and other drugs (1,2).

Two interpretations have been proposed to explain this correlation: 1) adolescents who become drug involved are vulnerable because of the combination of inherited impulsive, risk-taking behavior, family history, and challenging social environment, which includes access to drugs, and 2) exposure of the developing brain to addictive drugs during the critical final phase of brain development causes permanent changes in the brain that render the individual more vulnerable to addiction. Although numerous studies in humans support the former possibility, an emerging body of animal studies suggests that drug action on the brain itself has persevering effects that contribute to the progression of addiction into adulthood. The article by Cass *et al*. (3) in the present issue addresses this possibility.

The groundbreaking studies of Jay Giedd and colleagues have shown that the developing forebrain is still undergoing remarkable structural maturation during adolescence (4). Studies have shown that the subcortical reward system holds greater sway over adolescent decision making than the immature amygdala-cortex axis, which monitors risk and attributes emotional salience to events. The prefrontal cortex, which exerts executive control over these inputs, is hypofunctional in adolescents relative to adults (5). Adolescent rodents, like humans, exhibit exaggerated dopamine responses to reinforcers and are guided more by reward than punishment during this critical developmental epoch (5,6). A small but crucial number of animal studies have shown that numerous elements of cortical structure and function could contribute to this adolescent vulnerability, including rapidly evolving responses to dopamine and a relative lack of inhibitory control by gamma-aminobutyric acid (GABA)-ergic interneurons (7).

This different balance of reward, risk, and executive function in adolescence may provide an understanding of why adolescents might experiment with drugs and find them reinforcing,

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but it does not address the more troublesome question of whether adolescent drug exposure per se increases the risks of addiction or other adverse behavioral outcomes in adulthood. Rodent studies of the consequences in adulthood of addictive drug self-administration during adolescence have resulted in contra-dictory findings about whether early consumption of nicotine, alcohol, cocaine, or tetrahydrocannabinol increase or decrease the risk of addiction later in life. Furthermore, we have little mechanistic understanding of what brain changes result from these exposures and contribute to adult behavior.

The study by Cass *et al*. in this issue (3) addresses a gaping hole in our understanding of whether or how early exposure to addictive drugs influences how the adult brain functions. They studied a logical but neglected target: the fast-spiking GABA interneurons in the medial prefrontal cortex (mPFC) which provide rapid and precisely-timed inhibition to gate the excitatory activity of cortical pyramidal cells. The mPFC is critically involved in working memory and decision making, and is disrupted by cocaine addiction. Furthermore, this disruption is thought to contribute to craving and relapse. Previous studies have shown that dopamine neurons innervate the fast-spiking GABA interneurons in this part of the cortex, and that cocaine modulates their activity (8). Furthermore, prenatal cocaine exposure has persevering effects on activity of these neurons (9). The authors have shown in the present study that adolescent but not adult cocaine exposure leads to a disinhibited state in the mPFC. They showed that adolescent cocaine exposure decreases the ability of critical inputs from the hippocampus to inhibit the cortex, and in fact, these neurons become more likely to cause sustained excitation after adolescent cocaine exposure. In addition, in exposed animals, the most rostral part of the cortex is metabolically hyperactive well into adulthood, long after cocaine exposure has ended. A comparable cocaine exposure in adulthood does not have these effects, a crucial control often omitted in such studies. This result was noteworthy because cocaine exposure is capable of influencing function of these neurons: its absence here indicates that cocaine has unique developmental effects due to exposure during a critical developmental window. Furthermore, they identify a possible mechanism by which this happens by showing that a GABA antagonist mimics and a GABA agonist reverses these changes. What is particularly novel about this finding is the previously neglected target. Most focus on cocaine action in the cortex has been on the pyramidal cells that provide its major excitatory output. However, the interneurons play a critical role in providing time-locked restraint on the pyramidal cells. Furthermore, their maturation is one of the final developmental events during cortical maturation that is thought to contribute to the maturation of adult decision making. It is hoped that future studies will identify the molecular changes responsible for this enduring change in brain function.

Although Cass *et al*.'s (3) study did not evaluate the behavioral outcome of the cocaine treatment, their results predict the (testable) possibility that adults who used addictive stimulants in adolescence may be more impulsive and exhibit impaired decision making, behavioral characteristics that are known to be associated with drug addiction. The present study has clearly opened an important window into a neglected target that can help explain adolescent addiction and potentially identify future treatments.

One of the controversial questions raised by these studies is whether exposure to nonaddictive stimulants such as methylphenidate that are used to treat attention-deficit/

hyperactivity disorder would have similar effects. The animal literature about the behavioral consequences of adolescent psychostimulant exposure is mixed, with differences in route of administration, window of exposure, and dose likely contributing to contradictory findings. Both increased and decreased risk of addiction to other drugs have been reported after adolescent methylphenidate exposure. However, studies that come closest to matching human exposure (low doses, oral administration, and long-term exposure) have been least likely to show enhanced self-administration of other addictive drugs (10).

In closing, we express a simultaneous note of reassurance and caution. The majority of adolescents mature into adults who do not abuse drugs; drug use of all kinds peaks in early adulthood and then falls, and animal studies show that the normative pattern similarly trends toward decreased consumption of alcohol, nicotine, and cocaine as animals mature (11). However, for vulnerable adolescents who have significant drug exposure in adolescence, the Cass *et al*. (3) study raises the concern that long-lasting effects on the part of the brain that we rely on for our most sophisticated thinking may be changed permanently by this exposure. Future research must answer the question of how the changes in cortical inhibition shown in the present study contribute to adult decision making.

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