Cannabis and the adolescent brain

With the use of legal marijuana proliferating, many want to understand the potential risks to teen users in particular. But thus far, definitive answers about the drug's effect on young brains have been hard to come by.

Helen Shen, *Science Writer*

For a developmental neuroscientist, Kuei Y. Tseng gets recruited to deliver a lot of talks to the public. Parents, educators, law enforcement, and teenagers all want Tseng to educate them about a hot-button issue: how cannabis affects the adolescent brain.

Tseng, based at the University of Illinois in Chicago, investigates how rats respond to THC (tetrahydrocannabinol), the main psychoactive ingredient in cannabis. He's found that exposure to THC or similar molecules during a specific window of adolescence delays maturation of the prefrontal cortex (PFC), a region involved in complex behaviors and decision making (1). The disruption alters how the area processes information when the animals are adults.

Audiences of parents and teachers tend to be alarmed by the long-lasting deficits, Tseng says. But when he speaks with teenagers, especially those already using cannabis, he gets a different response. "It's surprising, but they're not that worried." Youths often want to know how much cannabis they can consume without harming brain development; they press Tseng to extrapolate from rats the age at which it's "safe" for people to start using the drug. "They need to understand this is not black and white," says Tseng.

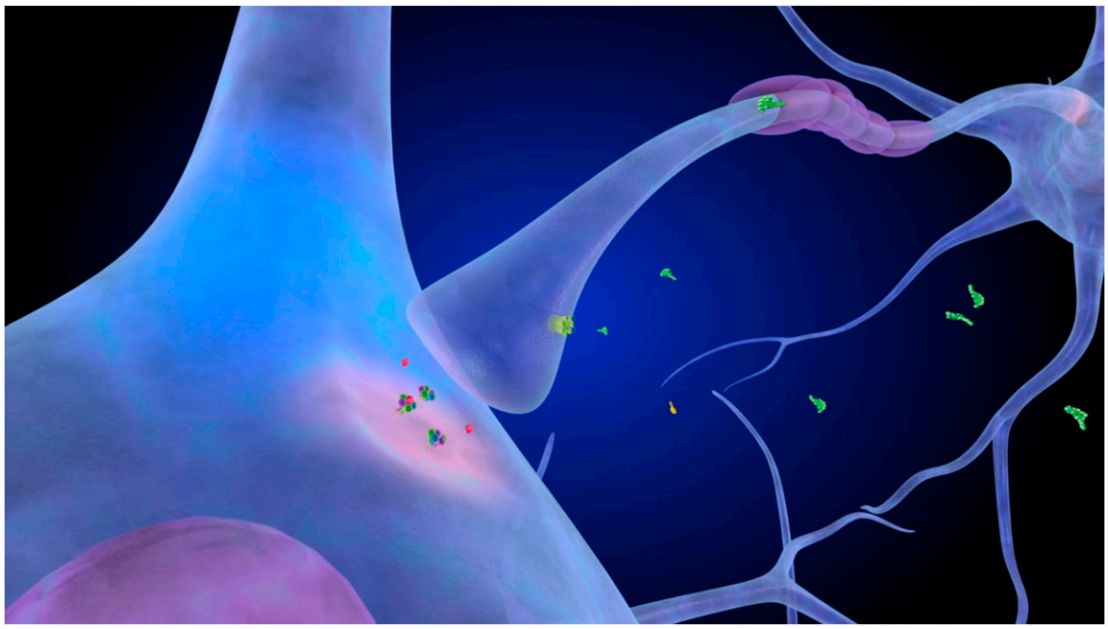
Nevertheless, some policymakers are already urging caution. In an advisory released August 29, the US Surgeon General went so far as to state that "until and unless more is known about the long-term impact, the safest choice for pregnant women and adolescents is not to use marijuana." At a luncheon in May, former US Food and Drug Administration (FDA) commissioner Scott Gottlieb said he had significant concerns about the "great natural experiment we're conducting in this country by making THC widely available," citing his fears about "the impact that this has on developing brains."

The question of safety for young users has taken on particular urgency in the United States, where, since 2012, 11 states and the District of Columbia have legalized the use of recreational marijuana by adults. Although it remains illegal for minors, the changing legal and commercial landscapes raise the possibility that cannabis products may also become more accessible and attractive to teens.

Most researchers stress that despite increasingly relaxed societal views toward marijuana, cannabis use—especially in adolescence—is not benign. Image credit: Shutterstock/Yarygin.

Despite such worries, definitive evidence remains elusive. Many observational studies have suggested that adolescent cannabis use may be linked to long-term harms, including cognitive impairment and increased risk of schizophrenia (2). But in almost every area that researchers have examined, results have been inconclusive regarding the precise nature and strength of these associations. In particular, there's little consensus as to whether cannabis directly causes long-term health harms in people, whether it's one of a number of risk factors, or whether it simply correlates with other root causes.

Ultimately, most researchers stress that, despite increasingly relaxed societal views toward the drug, cannabis use—especially in adolescence—is not benign. Many say that public health messaging should encourage teens to abstain from cannabis use as long as possible. A host of unanswered questions remain: What specific harms can individual users expect if they



THC (green, right and center) can bind to endocannabinoid receptors (yellow-green bundle, center) on the surface of certain neurons and affect their activity, including the neurons' release of GABA (magenta, left), which then regulates the activity of other types of neurons. Image credit: National Institute on Drug Abuse.

start using in adolescence? Are only certain people susceptible to potential ill effects? Is there a threshold age, or degree of cannabis use, that is safe or safer? Is cannabis-related damage reversible over time?

"We still don't have a handle on how THC affects the adolescent brain. There's a lot of evidence pointing toward negative outcomes, but more research needs to be done," says neuroscientist Jodi Gilman at Harvard Medical School in Boston, MA. "The policy is ahead of the science."

Many researchers are looking toward an ambitious initiative, now getting underway at the National Institutes of Health (NIH) in Bethesda, MD, to help bridge that gap. Touted as the largest long-term US study of brain development and child health, the project will collect a wealth of information—genetics, brain imaging, cognitive tests, daily habits, and more—on nearly 12,000 children, and aims to follow them into early adulthood over the next decade. "It's got so much potential to give us so much insight into the developing brain," says cognitive neuroscientist Catherine Orr at the Swinburne University of Technology in Melbourne, Australia. In the meantime, researchers are trying to make sense of the existing data and push the research forward—despite practical limitations on investigating the effects of marijuana in teens.

Revealing Rat Data

Many observational studies in humans imply a link between teen marijuana use and poor outcomes but are clouded by several potential confounding variables, such as socioeconomic circumstances or family mental health history. To better understand how cannabis affects the brain itself, some researchers have turned to controlled drug experiments that, for ethical and scientific reasons, can only be done in animals. What researchers really want to know is whether adolescent THC exposure could cause outsized neurobiological harms.

During adolescence, the brain undergoes major remodeling, especially in the PFC—one of the last brain regions to fully mature. In humans, this area is involved with high-level functions such as making decisions, controlling impulses, maintaining attention, planning, and working toward goals. The PFC also plays a role in defining our personalities and helps us understand and respond appropriately to social situations (2).

The adolescent PFC is a hotbed of synaptic reorganization. Excess neuronal connections are eliminated; other connections are stabilized. At the same time, many neurotransmitter systems are turning up or down production of signaling chemicals and adjusting the distribution of receptors for those molecules in different brain regions. Both of these processes are thought to facilitate efficient neural communication and help the brain transition from an immature to an adult state (3). All of this activity has led to the theory that the adolescent brain could be especially vulnerable to insults such as stress or drugs (4).

THC could be disruptive because it binds to the CB1 receptor, which is designed to respond to naturally occurring endocannabinoids (named for their chemical similarity to compounds in cannabis). Endocannabinoids play many roles, including regulating stress, fear, anxiety, mood, appetite, and pain (5–8). In the fetal brain, endocannabinoids modulate several developmental processes, and growing evidence suggests that they have a similar function in adolescence as well, influencing brain maturation (2, 5).

Supporting this idea, Tiziana Rubino at the University of Insubria in Varese, Italy, and her colleagues reported

in 2015 that THC exposure in adolescent female rats disrupted the maturation of multiple neurotransmitter systems in the PFC. In adulthood, PFC neurons in these animals were less adept at rapidly adjusting their connection strengths—a key process in learning and memory. When faced with a maze-learning task, the rats performed worse than control animals (9).

And some of THC's effects on brain development may be limited to specific windows of vulnerability, Tseng has found. Giving rats a THC-like synthetic cannabinoid during early and mid-adolescence—but not late adolescence or adulthood—interfered with GABA (gamma-aminobutyric acid), a major inhibitory neurotransmitter, in the adult rat PFC. (Based on neurodevelopmental stages, the equivalent cutoff age would be about 16 or 17 years in humans, says Tseng.) As a result, the adult PFC failed to develop certain patterns of electrical activity typical of the mature brain, suggesting delayed brain development (1). "There are a lot of psychiatric disorders that happen when the brain is transitioning to maturation," says Tseng. "Somehow, exposure to cannabinoids makes that window of maturation much longer than normal and might increase susceptibility to the onset of psychiatric disorders happening."

At Western University in London, Canada, neuroscientist Steven Laviolette's group has also found that exposing adolescent rats to THC impairs GABA signaling in the PFC when the animals become adults. This disinhibition of the PFC also leads to overactivity in dopamine neurons in a brain region involved in motivation and reward processing (10). Similar features have been observed in the brains of people with schizophrenia, notes Laviolette.

"Clearly there's something unique about the adolescent brain that makes it specifically sensitive to THC," says Laviolette. There may also be genetic variations that make some teens more sensitive than others to these effects. But the precise mechanisms that underlie both aspects of susceptibility are still unknown. "That's the next big thing to figure out," he says.

Cause and Effect Conundrum

Although animal studies like these have revealed several potential mechanisms by which cannabis might do harm, it's hard to determine what this means for human teens. Increased risk of psychiatric disorders is a major concern, with schizophrenia having attracted the most attention and controversy. In double-blind, placebo-controlled studies, intravenous doses of pure THC have induced temporary symptoms resembling some aspects of schizophrenia (11, 12). But researchers are still trying to establish whether cannabis use, especially in adolescence, could lead to full-blown schizophrenia in the long run.

In a landmark 1987 study, researchers reported a link between cannabis use and schizophrenia risk among more than 45,000 Swedish military conscripts who were examined at the time of conscription around age 19 and again 15 years later. Those who had used cannabis more than 50 times before conscription were six times more likely to be diagnosed with schizophrenia by the 15-year mark. The association was weaker, though still present, after controlling for factors such as adverse childhood conditions and diagnosis of other psychiatric disorders at the time of conscription (13).

In the decades that followed, several studies yielded similar associations. In one oft-cited 2002 study, psychiatrist Robin Murray at King's College London and his colleagues analyzed data from roughly 760 New Zealanders who had been followed since birth in the 1970s as part of a larger project, called the Dunedin Study. They found that starting cannabis use by age 15 was associated with a fourfold elevated risk of developing schizophrenia by age 26, whereas starting closer to age 18 carried only a small, nonsignificant increase in risk (14).

Heated debates linger over how to interpret such observations. "Most people would agree there's clearly a relationship that exists between cannabis use and schizophrenia," says neuropharmacologist Matthew Hill of the Hotchkiss Brain Institute at the University of Calgary. "I think it's the directionality of that relationship that's contentious."

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> **—Steven Laviolette**

Theories abound, but the available data are inconclusive, leaving researchers to argue about whether cannabis can directly cause schizophrenia (Murray believes it can, especially with heavy use), or primarily triggers or accelerates schizophrenia in a subset of people already predisposed to developing the disorder. Many researchers favor the latter theory, which, according to Hill, could help explain why rates of cannabis consumption in the Western world have increased dramatically since the 1960s but rates of schizophrenia (often cited to be around 1% or less) have not changed much over time (15, 16).

It's also possible that other factors contribute to the observed correlations. For example, some research suggests that people already predisposed to schizophrenia are more prone to use cannabis. In a sample of more than 2,000 healthy adults, one study found that those with gene variants linked to increased schizophrenia risk were more likely to use cannabis, and to use more of it than others. "This is not to say that there is no causal relationship between use of cannabis and risk of schizophrenia," the authors concluded. "But it does establish that at least part of the association may be due to a causal relationship in the opposite direction" (17).

Complicating matters, the neurobiological mechanisms behind schizophrenia itself are not well understood, and a number of other factors—including family life, smoking and alcohol use, educational experience, and more—can influence mental health outcomes. "As long as you're studying humans, there's always going to be the problem of real life,"

says Orr. "Each person is unique and accumulates circumstances before the study and during the study."

Cognitive Clues

Among many parents, educators, and policymakers, cognitive impairment, not mental illness, is the biggest concern. But once again, observational research has not provided definitive answers about whether cognitive changes associated with cannabis use are temporary, or at some point might become irreversible.

"There have been a couple studies that have gotten a lot of headlines that have not replicated well," says Hill. "I don't think there's any compelling evidence that moderate levels of use are going to produce long-lasting cognitive deficits."

In 2012, one high-profile study used the Dunedin Study data to compare people's intelligence quotient (IQ) between ages 7 and 13 (before cannabis use) and at age 38, and assess their drug use at various ages. Regular users of cannabis saw IQ declines between childhood and adulthood, whereas nonusers did not (18). A persistent cannabis dependence was associated with a loss of up to six IQ points on average, with deficits especially pronounced in those who became dependent before age 18. However, in 2018, the same research group concluded that cannabis use was not the cause of IQ declines during adolescence, even in dependent users, based on tracking a cohort of twins in England and Wales from age 5 to 18. Instead, they found that "family background factors" likely explained why the adolescent cannabis users performed worse on IQ tests (19).

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In the short term, research led by neuropsychologist Randi Schuster at Massachusetts General Hospital in Boston has found that certain cannabis-related cognitive losses may be reversible. Among regular users aged 16 to 25, those who cut out cannabis for four weeks saw improvements in verbal memory—especially during the first week (20). "We don't know how long it would take for them to reach—or if they would reach—the level of a nonuser," says Gilman, one of the study's authors. "But we found that continued use is worse than stopping."

Different methods are likely at the root of some of the mixed results. Studies often sample different age groups, or people with varying levels of drug use, and examine them for different durations, ranging from weeks to decades (21). As in the case of schizophrenia, the bulk of the human research is observational, yielding correlations but not proving causation. However, randomized controlled trials, the gold standard for resolving many types of biomedical questions in humans, are limited by ethical requirements that make it difficult to experimentally administer cannabis to teens.

Many researchers view the NIH's new large-scale prospective study as the next best thing. Besides schizophrenia and cognition, the Adolescent Brain Cognitive Development (ABCD) study could potentially clarify the role of adolescent cannabis use in other conditions, such as addiction or mood disorders.

Clearing the Haze

Interest in all these questions has intensified in recent years. As more states legalize marijuana for adults, some worry that young people will have greater access to and appetite for the drug. But it may be too soon to tell. A handful of early surveys in different states where recreational marijuana use was legalized, often using different sampling methods, have reached differing conclusions about whether youths perceive marijuana as less harmful, or are using it at higher rates after legalization (22–24). In November, a study of Colorado, Washington, Alaska, and Oregon found no changes in the rates of adolescent marijuana use after legalization, but did observe a slight rise in rates of cannabis use disorder among teens—though investigators couldn't rule out the influence of factors other than legalization, such as higher potency (25).

Despite lingering uncertainties, Nora Volkow, director of the National Institute on Drug Abuse in Bethesda, MD, says that there is enough information to be concerned. "The problem with marijuana is that we have data right now that go in all directions. What we're doing is building a study to answer the question of whether use of marijuana in adolescence affects the structure and function of the human brain, and whether it actually leads to cognitive or psychotic disruption," she says, adding, "There's urgency to establish this."

The ABCD study (26) completed enrollment in 2018, recruiting nearly 12,000 children aged 9 or 10, and will follow the children through roughly age 20. Researchers at 21 institutions around the United States have already collected the baseline brain images, genetic information, and neuropsychological, behavioral, and many other health measures. Over time, the project aims to characterize normal adolescent brain and cognitive development and tease apart multiple factors that can influence those processes, such as screen time, sports injuries, and—importantly—substance use.

By starting at a relatively young age and taking a diverse demographic, geographic, and socioeconomic sample, researchers intend to capture detailed information on circumstances that precede substance use and could influence risks (27). And by including 2,100 people who are either twins or triplets, they plan to compare many cannabis-using and nonusing siblings, to isolate the effects of genetic and family factors. Such comparisons could also help reveal whether some youths are more predisposed than others to use cannabis or are more vulnerable to its effects on the brain.

It will be years before the ABCD study finishes, and even then it's unlikely to settle all of the current questions and debates, as some researchers note. Although few researchers dismiss the potential for cannabis to harm the developing teenage brain, much remains unknown. Many see the project's size, duration, and depth as a big step toward understanding important particulars. Such studies, says Gilman, "will go a long way to clearing things up."

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