



## WHAT WERE WE TALKING ABOUT?

**DOES ADOLESCENT USE  
OF MARIJUANA STUNT BRAIN  
DEVELOPMENT AND OPEN  
THE DOOR FOR PSYCHOSIS?  
BY DAVID R. ELTZ**

**L**et's say you're starting your first day as an intern at a software company. In 20 minutes your boss meets with the senior partner, and he's just finished polishing a product proposal that could earn the company millions ... and put him in line for the division vice president position.

He e-mails the proposal to you, with directions to print 10 copies and staple and deliver them to his desk in five minutes.

ILLUSTRATION | NICOLE FICHERA

Excited, you send the document to the printer, jump from your chair, and rush to retrieve the printouts, running the instructions through your brain. Oh. And you've recently been diagnosed with schizophrenia and can't help but think you need this internship amid the daily struggle to keep your mind focused, away from your occasional debilitating delusions, hallucinations, and depression.

You take with you all your hope for a normal life and normal thoughts along with

aim to find out by testing the brains of adolescents before they start using marijuana.

They wonder: Does using marijuana early in adolescence cause some kids to eventually develop schizophrenia, the most common psychosis in the world? Did the kids who have impaired working memory have those problems before they started smoking marijuana? If marijuana is a catalyst, does it change something in the brain, or is the change an indirect consequence of something else?

oping, particularly before the age of 16. In the United States, about 6,000 people start smoking pot every day, or about 2.1 million every year. Most are under the age of 18.

Many researchers believe that using pot while the brain is still developing boosts levels of the chemical dopamine in the brain, which may directly lead to schizophrenia—although moderate amounts of the chemical are essential for brain health. Others believe that kids who smoke pot and harbor the variant of a gene

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your boss' instructions. But when you grab the printouts from the tray, you suddenly freeze, thinking, *Now what was I supposed to do with these?* The rest of the instructions are gone, wiped from your brain.

What's happened to you, a failure of a brain process called working memory, is similar to what occurs when someone high on marijuana says, *Dude. What were we talking about?*

Your brain is an orchestra, with highly specialized subsections playing in tune, under the direction of a conductor delivering a central timing signal. In schizophrenia, and in people who smoke pot, the timing is "off." Specifically off: working memory, the core cognitive process that allows you to keep a limited amount of information in your head and follow a logical path—like a set of instructions—without having to, say, stop and wonder what you were supposed to do after printing a document.

Researchers have known for a while that people with schizophrenia and marijuana users share working memory impairments. But they've always measured those impairments after smokers and schizophrenia patients had already exhibited problems with working memory. So how did they get the impairments?

David Lewis, UPMC Endowed Professor of Translational Neuroscience and chair of Pitt's Department of Psychiatry, and colleagues

"Maybe it's starting to use marijuana early, and then the kids get unmotivated," says Lewis. "They don't go to school. They don't engage in cognitively challenging activities. And the absence of practice means that their neural circuits don't develop properly."

In other words, if you don't use it, you might lose it, and then maybe your brain becomes susceptible to psychoses like schizophrenia.

When people smoke marijuana, their lungs quickly absorb the psychoactive chemical THC. Just as fast, THC infiltrates the bloodstream and races to the brain, attaching to cannabinoid receptors, throttling the regions of the brain that control sensory perception, motor control, pleasure, and memory.

They are high within minutes because their brains stop working the way they should.

During that high, marijuana disrupts neurotransmitter paths essential for memory and decision making. What results is uncoordinated and inaccurate brain activity, similar to what goes on in the brain of someone with schizophrenia.

The use of marijuana or other forms of cannabis has been linked with a significantly increased probability of developing schizophrenia in multiple studies. Many of the studies suggest the risk is higher when adolescents use marijuana while their brains are still devel-

oped.

Studies have also found that people with schizophrenia are about twice as likely to smoke pot as those who don't have the disease. (In people with schizophrenia, cannabis can enhance mood while dulling hallucinations and delusions before eventually making these symptoms worse.) Meanwhile, those who smoke pot seem to be two or three times as likely to develop psychosis as people who don't.

In work funded by the National Institute on Drug Abuse, Lewis has already discovered that one neurochemical system of the brain affected by pot, the endocannabinoid system, is altered in people with schizophrenia. The change happens in the prefrontal cortex (the gray matter behind the forehead) and contributes to changes in the transmission of GABA, an important molecule that determines not only how active brain neurons are but also when they are active. If GABA production is disrupted, and either too much or too little is in your brain, the timing of your brain function is off.

"Lots of things don't work right," Lewis says. "And in the prefrontal cortex, if the timing is off, then abilities like cognitive control and working memory are disrupted."

That is, in the orchestra inside your brain, the horns play out of sync. The cellists come in too soon. The violins hold their notes too long. The orchestra dissolves into cacophony,

and the conductor, GABA, can't bring the musicians under control.

In animal studies, Lewis found that the cannabinoid 1 (CB1) receptor, the principal target of both THC in marijuana and the brain's own endocannabinoids, was present in lower amounts in mice that had less GAD67, the enzyme that makes GABA. Activation of CB1 receptors suppresses GABA release. These findings suggest that the lower levels of CB1 receptors in schizophrenia were compensating for deficient GABA in the illness. This could mean that when people with schizophrenia smoke pot, they essentially flood the brain with THC, which binds to the CB1 receptor and robs the brain of this compensatory mechanism.

"This may explain why when people who have schizophrenia are hospitalized, they get better, they're discharged; then they start using marijuana, and they get worse," says Lewis.

**A**dolescence is a key period in which the brain undergoes extensive remodeling. Our neural networks receive an upgrade then that we continue to depend on throughout our lives. To try to determine whether marijuana short-circuits that network and leaves kids susceptible to psychoses like schizophrenia, Pitt researchers are studying kids at 12—before they start using marijuana—and again when they

are 16. (In case you're wondering: No, the researchers won't be giving the kids pot. In fact, they're also embarking on a pilot project to reduce teenage marijuana use.)

For the study, currently funded by a tobacco settlement grant from the Commonwealth of Pennsylvania, Nancy Day, Pitt professor of psychiatry and epidemiology, is recruiting 100 kids. Day's earlier work found that adolescents born of women who smoked pot during pregnancy have problems with attention, impulsivity, depression, and school achievement. Based on previous research, she expects as many as 50 percent of the kids will start using marijuana during the new study.

Pitt researchers plan to follow the kids throughout four years, initially measuring baseline cognitive performance while they play spatial delayed-response games that require working memory, like trying to remember where a circle should be on a computer screen after seeing it disappear 30 seconds earlier.

While the kids perform the tasks, Beatriz Luna, Pitt professor of psychiatry and of psychology and director of the Laboratory for Neurocognitive Development at the Western Psychiatric Institute and Clinic, will measure brain function using functional MRI (fMRI). Luna, whose work explores the role an adolescent's developing frontal cortex plays in executing cognitive tasks, will take baseline neuroimaging snapshots of the

kids' working memory.

Raymond Cho, Pitt assistant professor of psychiatry and of psychology, will use electroencephalography (EEG) to measure rhythmic brain waves called gamma oscillations, which are highly dependent on GABA, the brain's primary inhibitory neurotransmitter.

After four years, the kids are to perform the tasks again, during fMRI and EEG tests. And the researchers will look for changes between the earlier, baseline measurements and the second set of images that indicate slow and uneven development or disrupted brain waves.

"First we determine [how their working memory is] when they're young," says Luna. "Then, when they come back at an older age, some of them would have had exposure to cannabis, some would not, and then we can very nicely start to see if there has been a toll on working memory."

Lewis will mirror his colleagues' work with kids in a study of adolescent monkeys, some given intravenous THC daily. The monkeys will perform spatial delayed-response tasks similar to those undertaken by the kids while also having working memory measured by EEG.

Will the kids and young monkeys exposed to THC both develop deficiencies in working memory? If so, it will lend credence to the hypothesis that THC in pot disrupts adolescent development of orchestral neural circuits, leading to cognitive impairment. ■

## WHAT YOU DON'T KNOW CAN HURT HIM

Peter Tosh urged, "Don't criticize it." And Black Sabbath sang of the "sweet leaf." Yet what might have once seemed like merely a playful indiscretion—toking up—may have debilitating repercussions in youth. Scientists at Pitt and elsewhere are investigating apparent links of cannabis use in teens with cognitive impairments, and even with schizophrenia.

So how does a parent or pediatrician intervene? Teenagers, by nature, are secretive when it comes to telling parents about experimenting with risky behaviors. And pediatricians don't have much time during an office visit to gauge the risk for marijuana use and intervene.

Duncan Clark, Pitt associate professor of psychiatry, hopes to change that. Clark is researching the best way to build an intervention program. He envisions teens and their parents, while in a doctor's waiting room, answer-

ing questions on a tablet computer about risk factors for later experimentation with pot. The software would immediately generate an assessment for the pediatrician before the teen walks into the examination room, so the doctor would know if the adolescent is likely to try smoking pot. Whether the adolescent is at risk—or probably already smokes marijuana—the doctor could take steps to help the child stop smoking pot. The pediatrician would also give parents pamphlets from the National Institute on Drug Abuse ([www.drugabuse.gov/marijbroch/parents](http://www.drugabuse.gov/marijbroch/parents)) that can help them talk to their son or daughter about the dangers of marijuana.

Clark says he'll be using focus groups in the next few years to develop the program. He has already tested similar software that assesses teenage alcohol use, which happens to be a risk factor for later smoking pot. —DE