Project explores how cannabis may affect men and women differently

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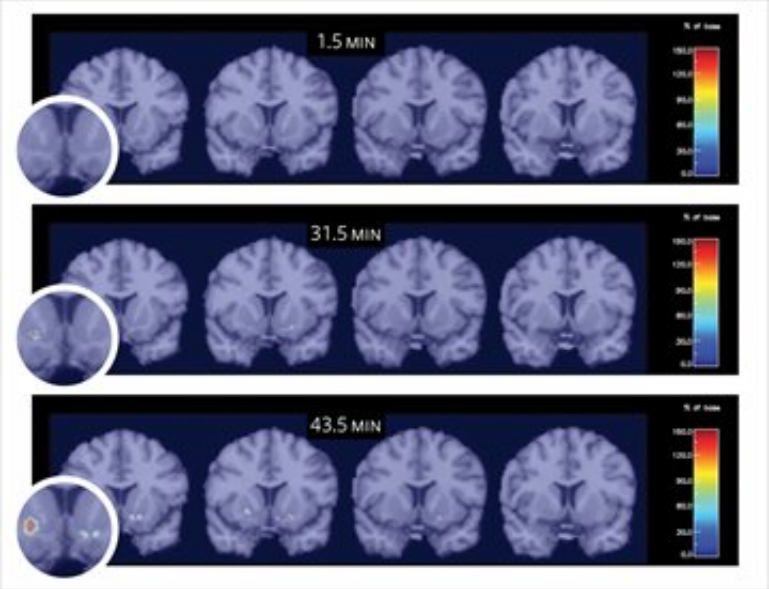

Dr. Cosgrove's research team uses a mathematical model to take images from PET and MRI scans and create unique videos, shown in segments here, that depict dopamine activation before, during, and after smoking cannabis. Credit: Yale University

Jessica usually smokes cannabis five days a week, mostly at the end of the day, often while reading. "Why do some people drink alcohol?" she said. "It's a way to come down after a hectic day. I treat it more like a beer with dinner."

But one morning late this winter, she smoked a cigarette rolled with

government-grown cannabis while lying with her head inside a scanner that recorded images of a radioactive tracer's path through her brain. "Cannabis has been illegal and impossible to study," said Jessica, a 25-year-old graduate student. "The more we know about it, the more we understand how it affects us. It's not something that's going to go away."

Even as the federal government treats the possession and use of cannabis as illegal for any purpose, 29 states now allow medical use of the drug, and nine states have authorized it for recreational purposes. This new and rapidly evolving legal landscape arrives with many unknowns, not the least of which is how, precisely, this popular illicit drug affects people's brains and behavior.

Jessica, not her real name, was one of the first subjects participating in a study funded by Women's Health Research at Yale using a new brain scanning technique to examine for the first time how smoking cannabis affects the brains of women and men.

About half of all Americans have tried cannabis, with 22 million reporting they have used it at least once in the last month. Use of the drug is particularly common among adolescents and young adults, whose brains are still developing.

And newer generations of cannabis users are consuming the drug with a potency that has greatly increased over the years. In confiscated samples of cannabis, the average content of tetrahydrocannabinol (THC), the major psychoactive ingredient, climbed from 4 percent in the early 1990s to 12 percent in 2014.

Varieties available in flower form at Connecticut dispensaries—sold with a doctor's certification to patients with qualifying diagnoses such as cancer, glaucoma, AIDS, Parkinson's disease, multiple sclerosis, epilepsy, and post-traumatic stress disorder—can have THC contents

well above 25 percent. Concentrated forms such as oils and resins approach and exceed 90 percent THC. Other varieties are lower in THC and higher in other compounds, such as cannabidiol (CBD), which has been used to calm anxiety and suppress seizures, particularly in children, without a psychoactive effect.

Greater potency carries the potential for greater problems. About 4 million Americans meet the diagnostic criteria for a marijuana use disorder, meaning that due to their marijuana use they suffer from difficulties with health or the ability to meet responsibilities. The disorder can involve dependence—in which a user who stops taking the drug experiences withdrawal symptoms such as irritability, anxiousness, depression, and sleeping problems—and addiction, defined as the inability to stop even when use causes significant health and social problems in the user's life.

As recipients of WHRY's Wendy U. and Thomas C. Naratil Pioneer Award, the researchers expect to find a faster neurochemical reward response in women that makes women more susceptible to addiction and opens the door to the development of gender-sensitive addiction prevention programs and treatments.

"With so little research on this topic, I don't think we know very much at all," said Dr. Kelly Cosgrove, Associate Professor of Psychiatry, Radiology and Biomedical Imaging, and Neuroscience. "The first thing we need to do is nail down exactly how cannabis affects brain chemistry."

Cosgrove, the study's lead investigator, helped develop the brain scanning methodology in studies of tobacco smoking and alcohol dependence. She saw a clear parallel in adapting the technique to explore how cannabis works inside the brain and to eventually help design better, targeted treatments for people who develop dependence or addiction.

"Not everybody who smokes or consumes cannabis will develop a problem," she said. "But even if a small percentage of users develop a marijuana use disorder, that represents a lot of people we can help."

A Chemical Reward

In the brain, dopamine is the primary neurochemical for reward. As a neurotransmitter helping brain cells communicate with one another, it can create a sense of euphoria or of simply feeling good. The release of dopamine is what produces the good feeling when someone enjoys eating, having sex, acing a test, winning a race, hugging a baby—all of the activities the body naturally rewards.

But there can be too much of a good thing, particularly when it comes to ingesting substances. The "good feeling" associated with drugs such as nicotine and cocaine arrives in part from a release of dopamine in the brain, which diminishes with repeated use and can push people to seek the drug over and over again because the intensity and duration of the "good feeling" subsides over time. This pursuit of that feeling or effect can damage the user's health and happiness.

In studying cigarette smokers, Cosgrove and other researchers in the Yale Specialized Center of Research (SCOR) to Develop Gender-Sensitive Treatment for Tobacco Dependence discovered that men smoke more often for the rewarding effects of nicotine, and women smoke more often to cope with stress or otherwise improve their mood.

"We're starting to treat men and women cigarette smokers differently," Cosgrove said. "Men are more likely to respond to nicotine replacement therapy, for example. We are pursuing development of new medications targeted to help women. And that's because of the research we're doing."

Now Cosgrove wants to make a similar impact by informing people about the risks of using the cannabis of the 21st century and providing data-driven assistance for people who develop a cannabis use disorder.

"For example, if we find sex differences in marijuana smoking, it could lead to a different treatment regimen," she said. "Maybe women and men need different clinical interventions. We won't know unless we continue to study the issue."

Making Movies of the Mind

In order to determine how the brains of women and men react differently to drugs, researchers need the right tools and a way to analyze the data they obtain.

In studies exploring the effects of nicotine, alcohol, cocaine, and cannabis on the brain, Cosgrove uses images created by positron emission tomography (PET).

A PET scan allows researchers and medical practitioners to track chemical activity in the body that could be evidence of disease or—as with the cannabis study—of dopamine release. In this procedure, a team operating a PET scanner injects a safe radioactive drug, known as a tracer, into a subject or patient. The tracer is known to collect in the specific areas of chemical activity under study, and the radioactivity shows up visually as bright spots on the recorded images to aid diagnosis or provide useful data to researchers about how psychological processes or disorders affect brain activity.

For example, when men smoke cigarettes while in a PET scanner, dopamine gets released in a part of the brain called the ventral striatum, which is associated with reward and reinforcement. For women, dopamine tends to collect in the dorsal striatum, which is more

associated with habit and learned behaviors like those in response to a negative mood.

A WHRY study is using a new brain scanning technique to examine for the first time how smoking cannabis affects the brains of women and men. Credit: Yale University

This fits with other research revealing that men smoke more for the rewarding effects of nicotine and women smoke more to affect mood and are cued by other aspects of the habit than the craving for nicotine.

Traditionally, researchers using PET scans to detect the effect of a particular drug on dopamine activity in the brain first administer the drug, then place the subject in the PET scanner, wait 90 minutes, and calculate the average over that time of how much of the tracer binds to

the dopamine receptors they are targeting.

About 10 years ago, Dr. Evan D. Morris, Professor of Radiology and Biomedical Imaging, Psychiatry, and Biomedical Engineering, began looking at what valuable information might be hiding in that average.

"What happens if a phenomenon we're looking for happens in a short period of time?" Morris said. "What if there is a spike in the data and not a simple straight line? Can we detect these things? We needed a more sophisticated mathematical method."

Dr. Jenna Sullivan, in 2013 the first graduate student to earn a Ph.D. while conducting research in the Yale PET Center, wrote her doctoral thesis after discovering in papers published by others that the amount of time spent in the PET scanner after smoking affected the results.

"Timing mattered," Morris said. "The information we were seeking was in the data. It was just a matter of getting it out and getting it out reliably."

Morris and his students developed a mathematical model that reliably extracts the timing data and allows the team to map the dopamine activation before, during, and after a drug's administration. Currently, Heather Liu, a second-year biomedical engineering graduate student, helps crunch the numbers and create data visualization movies that depict precisely what is happening over time.

"If an effect is short, if it's subtle, a traditional model won't capture it at all," Liu said. "Dr. Morris' model is unique and gives us the entire curve of dopamine as it is released over time—not just before and after it is released."

Smoking for Science

When Jessica showed up for her PET scan, she had been asked to abstain from smoking cannabis for 12 hours to maximize any craving. With approval from Yale's Institutional Review Board to conduct research on human subjects, Cosgrove's team and the staff at the PET center took a detailed medical history and assessment of cannabis, alcohol, and other drug use.

They tested her blood for levels of hormones and THC.

They performed a physical and neurological examination, including an electrocardiogram of heart function to make sure she had no complicating medical conditions.

They screened her urine to make sure she wasn't pregnant.

They evaluated her to determine any psychiatric illness and assessed her for depression, anxiety, and impulsivity.

They administered a task designed to assess her responsiveness to rewards.

And they asked her to plunge her hand into freezing water to assess her pain threshold and any possible link to cannabis craving.

Jessica also underwent a magnetic resonance imaging (MRI) scan that the researchers used to map where the PET scan shows activity on a more detailed image of her brain.

After the battery of tests, Jessica lay down on a cushioned table with her head in the round opening of the PET scanner. A nurse infused her with the radioactive tracer through an intravenous tube. And after 30 minutes, she began to puff from a cannabis cigarette, provided through the National Institute on Drug Abuse, with about 3.5 percent THC, exhaling

into the bowl-shaped end of a device that sucked in the smoke and filtered it to protect the researchers and the equipment.

After each staggered series of puffs, a researcher asked Jessica to rank on a scale from zero to 10 how high she felt, how good she felt, how anxious she felt, and how much she was craving cannabis.

In a control room, computer monitors displayed the position of Jessica's head in the PET scanner and began to produce the numbers Liu will apply to Morris' mathematical model and translate into the videos showing where, when, and for how long the dopamine appears.

For most subjects, the dopamine starts to flow shortly before they begin to smoke. The researchers interpret this as anticipation of the pleasurable effects of the drug.

For this initial study, the team anticipates testing five women and five men. They expect to find a difference between the sexes and then apply for a larger grant to test more subjects, looking for a larger effect and eventually the proof necessary to guide better, more individualized treatments.

After a day of medical and psychological tests, smoking for science, Jessica reported feeling relaxed. A little sleepy, but satisfied she helped contribute to a better understanding that can help people.

"Men and women should be treated equally, but biologically we are separate," Jessica said. "Who knows what's going to be uncovered. It's why we need to keep looking."

Provided by Yale University