Over the past decade recreational/medicinal use of cannabis was legalized in the District of Columbia as well as in Alaska, Colorado, Oregon and Washington State; 19 other states also permit the use of the drug for medical purposes.

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On the street it’s called skunk for its intense, pungent odor. But the smell isn’t the only thing that’s strong about this type of marijuana. These increasingly popular strains contain
high levels of delta-9-tetrahydrocannabinol (THC), the main psychoactive substance in cannabis that causes its euphoric effects. Several new studies have noted the rapid rise in marijuana potency and raised questions about the risks it poses to users.

According to a recent analysis presented at the 2015 Meeting of the American Chemical Society, the amount of THC in samples from marijuana sold in Colorado are reaching 30 percent. “When I started to study marijuana in 1966, levels of tetrahydrocannabinol were 3 to 6 percent,” says Lester Grinspoon, an associate professor emeritus of psychiatry at Harvard Medical School and the American godfather of medical marijuana, “I’m amazed in the way marijuana has grown commercially—people who do grow it are trying to get strains with higher and higher levels of tetrahydrocannabinol.” This trend can also be seen in European countries. In a recent report researchers found that the concentration of THC sold on the streets in Denmark has tripled to an average of 28 percent in the last 20 years.

Attitudes toward marijuana are also rapidly changing. In the 1960s surveys found a mere 12 percent supported marijuana legalization—now, more than 50 percent are in favor. Over the past decade recreational/medicinal use of cannabis was legalized in the District of Columbia as well as in Alaska, Colorado, Oregon and Washington State; 19 other states also permit the use of the drug for medical purposes. As more states and countries, such as Canada and the U.K., consider following suit, advocates and critics are engaging in heated debates about the potential risks and rewards—particularly in light of the increasing prevalence of highly potent marijuana. But the evidence is nebulous—even within the scientific community, there is lack of consensus about how much harm marijuana can do to users’ brains and mental health.

In addition to THC, the other major component of marijuana that has caught the attention of researchers is cannabidiol (CBD), which scientists have linked to antipsychotic properties. Not only do THC and CBD have opposing effects, cannabis with higher THC content tends to contain lower amounts of CBD. “The relationship between CBD and THC is unique, in that the biological process required to make THC antagonizes the generation of CBD,” says Matthew Hill, a cannabinoid neuropharmacologist at the University of Calgary.

**Damage to the brain?**

In an article published last month in Psychological Medicine, researchers at King’s College
London and Sapienza University of Rome conducted a neuroimaging study to assess the effects of cannabis use on the corpus callosum, the largest collection of white matter in the brain containing fibers that facilitate communication between the two hemispheres. They found that this structure was negatively affected in those who used high potency cannabis—strains high in THC and low in CBD—compared with those who used lower strength bud or did not use at all. Moreover, the changes were similar in both those with and without previous episodes of psychosis. “I think it adds to our knowledge of what cannabis is potentially doing in the brain,” says Eden Evins, a psychiatry professor at Harvard Medical School who was not part of the research. “It’s a small study—I’d love to see a bigger study with more power [to control] for interactions—but it’s well done for its size.”

Although provocative, some researchers caution against jumping to conclusions. “We do not know whether the changes were present prior to the onset of marijuana use,” says Margaret Haney, a neurobiology professor at Columbia University who also did not take part in the study. This is possible because the study was cross-sectional—comparing nonusers to users rather than the before- and after-effects in each user. Critics also point to the additional variables to consider when interpreting this study. “They don’t distinguish alcohol use and other drugs between cannabis users and nonusers, and you have what could easily be an effect of multiple drugs at once,” Hill says. Although not reported, however, the researchers assert that they did take other drug usage into account. "Low- and non-users merged compared to high users did not differ in alcohol use or intake and drug use, but this analysis is not reported here in the paper," says Tiago Reis Marques, a senior research fellow at King’s College and a co-author of the study.

Previous studies have demonstrated the importance of these confounding factors when interpreting marijuana’s effects on the brain. For example, a 2014 study in The Journal of Neuroscience reported that marijuana use was associated with changes in brain structures associated with reward processing. This effect was dose-dependent, meaning the more cannabis someone used, the more changes became apparent in their brains. In a subsequent study, published in 2015 in the same journal, another group of researchers found that once variables such as alcohol use, gender and age were controlled for, the differences between users and nonusers disappeared.

The results of the current study, nonetheless, captured the attention of numerous news outlets—with some claiming that using highly potent marijuana can cause brain damage. “Of course, by definition correlation does not mean causality,” says Silvia Riguacci, a
neuroscientist at Sapienza and lead author of the study. “However, previous studies from our group showed that the risk of developing psychosis is greater, and onset occurs earlier, in those individuals who use more frequently and those who use cannabis with higher THC content.”

A cause for madness
In a study published earlier this year in Lancet Psychiatry the same group of researchers at King’s College assessed 780 people between 18 and 65 in London and reported that 24 percent of new cases of psychosis were associated with the use of high potency cannabis. Whereas this was one of the first studies to look at the link between highly potent marijuana and psychosis, researchers have found that using cannabis, and THC specifically, can produce acute psychotic symptoms, and some researchers suggest it increases the risk of developing schizophrenia. “There is an absolutely consistent association, there’s a dose-dependent response in terms of both frequency and potency and there’s biological plausibility,” Evins says. “There is a preponderance of evidence that leads up to the consensus that cannabis is a preventable risk factor for psychosis.”

The link between marijuana and psychosis, however, has been a matter of heated debate in the scientific community. Researchers have argued that there are sufficient grounds to doubt the causality of this link. There are two alternative possibilities: being predisposed to schizophrenia may increase the likelihood for cannabis use or a third variable may make it more likely for people to use marijuana and develop schizophrenia. For example, previous studies have suggested that schizophrenia and cannabis share both genetic and demographic risk factors, such as low socioeconomic status.

Critics also point to the fact that all the studies to date have been correlational. But this does not immediately dismiss the possibility that causation is possible. After all, although there was a strong correlational link between smoking and cancer, it took a study of more than 30,000 British doctors to confirm causality.

According to Haney, the odds ratio—the likelihood that an exposure will lead to a certain outcome—of marijuana causing psychosis are much lower than those for smoking and cancer. “There is also an association with tobacco smoking and schizophrenia that is much stronger [than cannabis use],” Haney says. “If this relationship is causal, it is a tiny effect, which might explain why there hasn’t been a dramatic upsweep in rates of schizophrenia
Both Haney and Evins agree that it is biologically plausible that marijuana, particularly at a young age, could increase the likelihood of negative psychiatric outcomes. The developing brain has an abundance of cannabinoid type 1 (CB1) receptors, where THC binds to exert its effects, in the prefrontal cortex, a key brain area impacted by schizophrenia. “I don’t think it’s a good idea for young children to be smoking marijuana at all because of their developing brains but I am extremely cautious about pinning it all on marijuana when there is a potential for many other explanations,” Haney says.

To truly determine whether marijuana causes such effects, scientists would need to track changes that occur in a large number of individuals before and after they use a drug over a long period of time. An effort to conduct this type of study is currently underway—the National Institutes of Health recently funded the multicenter Adolescent Brain Cognitive Development Study, which plans to recruit 10,000 children before they start drug use, and follow them for 10 years to assess the short- and long-term effects of using marijuana, tobacco and other drugs.

**Clearing the haze**

Cannabis has been found to impair cognitive functions such as memory and is increasingly being considered an addictive substance, especially in adolescents. There are still many questions that remain to be answered but strict regulation and lack of funding pose large barriers to conducting the required studies. The U.S. Drug Enforcement Administration still classifies marijuana in its most restrictive “Schedule I” category, which puts tight regulations on researchers who want to study its effects.

In the meantime scientists agree the highly potent marijuana may be better to avoid. Aside from potential long-term harm, receiving a high dose of THC can be especially risky for first-time users who are more likely to experience adverse effects such as panic or anxiety attacks. But even knowing the potency of a product, consumers might not always get what they ask for. Because of competing laws at the state and federal level, the quality of regulation varies largely between states and regions. Although THC potency labeling is mostly required for both medical and recreational products, it is not always accurate—a study published this June in *JAMA The Journal of the American Medical Association* revealed that of the 75 edible marijuana products (from 47 different brands) researchers assessed only 17 percent accurately labeled their THC content.
Across labs and in homes, marijuana remains a highly debated issue. "Marijuana is an extremely polarizing topic among scientists, more than any other drug," Haney says. "This is a giant sociological experiment we're undergoing with the increased legalization of medical and recreational marijuana, and there are a lot of [potential harms], but I'm less concerned about massive increases in rates of schizophrenia."

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