Effects of Marijuana On Brain, Body & Behavior

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Director
National Institute on Drug Abuse
Marijuana is the Most Commonly Used Illicit Drug In the U.S.

• Over 111 million Americans have tried it at least once

• An estimated 2.4 million Americans used it for the first time in 2012


Tetrahydrocannabinol (THC)
Active Ingredient in Marijuana
ADDICTION IS A DEVELOPMENTAL DISEASE
it starts in adolescence and childhood

Age at tobacco, at alcohol and at cannabis use dependence as per DSM IV

Percentage of U.S. 12th Grade Students Reporting Past Month Use of Cigarettes, Marijuana and Alcohol

Natural and Drug Reinforcers Increase Dopamine in NAc

Drugs of abuse increase DA in the Nucleus Accumbens, which is believed to trigger the neuroadaptions that result in addiction.

Di Chiara et al.
Constituents of MJ and the Cannabinoid System

- **Δ⁹-THC**: delta-9-tetrahydrocannabinol
- **Δ⁹-THCV**: delta-9-tetrahydrocannabivarin
- **Δ⁸-THC**: delta-8-tetrahydrocannabinol
- **CBG**: cannabigerol
- **CBN**: cannabinol
- **CBC**: cannabichromene
- **CBD**: cannabidiol

Diagram:
- Presynaptic
- NT vesicles
- NT receptors
- Calcium channel
- Lipid precursors
- EC degradation
- CB₁ receptor
- EC
- Post-synaptic
Cannabinoid Receptors Are Located Throughout the Brain and Regulate:

- Brain Development
- Memory & Cognition
- Motivational Systems & Reward
- Appetite
- Immunological Function
- Reproduction
- Movement Coordination
- Pain Regulation & Analgesia
Long Term Effects of Marijuana

Addiction: About 9% of users may become dependent, 1 in 6 who start use in adolescence, 25-50% of daily users

Estimated Prevalence of Dependence Among Users

* Nonmedical Use
Source: Anthony JC et al., 1994
Drug Use Outcomes in Twin Pairs (n = 234) Discordant for Cannabis Use Before Age 17

Does marijuana use negatively affect the developing brain and an individual’s personal trajectory into adulthood?
Cannabis Use and Later Life Outcomes Are Dose Dependent

- % welfare dependent (ages 21-25)
- % Unemployed (ages 21-25)
- Mean personal income in thousands of NZ $ at age 25
- % gained university degree by age 25

Early Marijuana Use and Intensity of Use are Associated with Educational Attainment

High School Completion

<table>
<thead>
<tr>
<th></th>
<th>Low Intensity</th>
<th>Med/High Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; Age 14</td>
<td>-12%**</td>
<td></td>
</tr>
<tr>
<td>&gt; Age 14</td>
<td>-1%</td>
<td>-11%***</td>
</tr>
<tr>
<td>-28%***</td>
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University Entrance Score

<table>
<thead>
<tr>
<th></th>
<th>&lt; Age 14</th>
<th>&gt; Age 14</th>
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<tbody>
<tr>
<td>Low Intensity</td>
<td>-2.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Med/High Intensity</td>
<td>-10.1%**</td>
<td>-1.9%</td>
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Young people who begin marijuana use at a young age and use it intensively have a higher probability of dropping out of high school.

For those that do successfully complete high school and obtain a university entrance score, med-high intensity use is associated with scores on average 10 percentiles lower than their peers.

*** p<0.01, ** p<0.05

Persistent Cannabis Users Show Neuropsychological Decline from Childhood to Midlife

**Dunedin**
prospective
study of 1037 Ss
born 1972/73,

**Tested for IQ at**
age 13 and 38y.

**Tested THC use**
ages 18, 21, 26,
32 and 38y

<table>
<thead>
<tr>
<th>Change in Full-Scale IQ (in standard deviation units)</th>
<th>1 Diagnosis</th>
<th>2 Diagnoses</th>
<th>3 Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis Dependent Before Age 18 (n=17)</td>
<td>p=.44</td>
<td>p=.09</td>
<td>p=.02</td>
</tr>
<tr>
<td>Not Cannabis Dependent Before Age 18 (n=57)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis Dependent Before Age 18 (n=12)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Not Cannabis Dependent Before Age 18 (n=21)</td>
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<tr>
<td>Cannabis Dependent Before Age 18 (n=23)</td>
<td></td>
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</tr>
<tr>
<td>Not Cannabis Dependent Before Age 18 (n=14)</td>
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</tbody>
</table>

Early (<18y) Long-Term Cannabis Use Decreases Axonal Fiber Connectivity

Axonal paths with reduced connectivity (measured with diffusion-weighted MRI) in cannabis users (n=59) than in controls (N=33). Zalesky et al Brain 2012.
AMOTIVATION & THC
Reduced striatal DA synthesis capacity in cannabis users relative to controls

Striatal DA synthesis and apathy (AES-S score)

Bloomfield et al., Psychopharm 2014.
Methylphenidate Induced Changes in $[^{11}\text{C}]$Raclopride (Dopamine Marker) in Controls and Marijuana Abusers and Negative Emotionality

Brain reactivity to DA stimulation by MP along with its behavioral and cardiovascular effects are attenuated in Marijuana Abusers; and their reduced DA reactivity in VS is associated with negative emotionality (NEM)

Volkow et al., PNAS 2014
Effects of THC on Mental Illness
Cannabinoid CB1 Receptors in Human Brain are Downregulated in Marijuana Abusers

Van Loere et al., 2007.  
Hirvonen et al., Mol Psychiatry 2013
Brain abnormalities associated with long-term heavy cannabis use

L (yellow) and R (blue) amygdala
L(red) and R(green) hippocampus

morphology and function of hippocampus has been linked to reduced memory performance in heavy cannabis users

Hippocampal and amygdalar volumes were smaller in cannabis users than in controls.

Yucel et al., Arch Gen Psychiatry. 2008 Jun;65(6):694-701.
Cannabis-Associated Psychosis

**Study of Swedish Conscripts (n=45570)**


![Graph showing the number of cases per 1,000 cannabis users by the number of times cannabis was taken.](image)

**Prospective Dunedin study (n=1037)**

Risk of schizophrenia-like psychosis at age 26 years

Arseneault et al BMJ 2002

![Graph showing the risk of schizophrenia-like psychosis at age 26 years among cannabis users.](image)

**Regular Cannabis Use Increases Schizophrenia Risk in those with AKT1**

Di Forti et al., Biological Psychiatry, 2012.

![Graph showing the odds ratio of schizophrenia risk for AKT1 genotypes.](image)

**Effect of High Potency Cannabis on Risk of Psychosis**

RM Murray, and M Di Forti Institute of Psychiatry, London UK

![Graph showing the adjusted OR for different levels of cannabis use and potency.](image)
THC OF TODAY
Increases over Time in the Potency of Tetrahydrocannabinol (THC) in Marijuana and the Number of Emergency Department Visits Involving Marijuana, Cocaine, or Heroin

Volkow ND et al., NEJM 370(23), June 5, 2014.
Mean Concentrations of THC, Ethanol & Amphetamines In Whole Blood Samples From Drivers Apprehended By The Police Suspected Of Driving Under The Influence

**Vindenes V et al., Forensic Sci Internati 2013; 226(1–3): 197-201.**
Proportion Of Drivers In A Fatal Motor Vehicle Crash Who Were Marijuana-Positive In Colorado and 34 States Without Medical Marijuana Laws From 1994-2011

12th Graders’ Past Year Marijuana Use vs. Perceived Risk of REGULAR Marijuana Use

Source: The Monitoring the Future study,

SOURCE: University of Michigan, 2013 Monitoring the Future Study
Prevalence of Cannabis Use among High School Students
Past Month Use, Percentages, 2007 and 2011

USA ranks 28th compared with 30 European countries.

Program for International Assessment (PISA) USA students ranked 35th in mathematics, 24th in reading, and 27th in science.
Adolescent Brain Cognition and Development
National Longitudinal Study
NIDA, NIAAA, NCI, NICHD

Ten year longitudinal study of 10,000 children from age 10 to 20 years to assess effects of drugs on individual brain development trajectories
Young Brains on Drugs

THE DEBATES OVER LEGALIZATION, DECriminalization, AND MEDICAL USES OF MARIJUANA IN THE United States are missing an essential piece of information: scientific evidence about the effects of marijuana on the adolescent brain. Much is known about the effects of recreational drugs on the mature adult brain, but there has been no serious investigation of the risks of marijuana use in younger users. In April 2014, a controversial study* suggested that "casual" use of marijuana is associated with structural abnormalities in the brains of young people (aged 18 to 25), particularly in regions vital to emotion, motivation, and decision-making. The fact that the findings are preliminary and disputed indicates that rigorous research is needed to inform discussions about the public health benefits and risks of legalized marijuana.

Although marijuana remains illegal for people under the age of 21 in the United States (including in the two states that have legalized it for adults), young people will almost certainly have greater exposure to, and likely more ways to access, the drug (as they already do with alcohol and tobacco), as new initiatives to change marijuana laws in many states come to fruition. Proponents of legalization argue that the medically harmful effects of marijuana are "no worse" than those of alcohol and tobacco. But even if that is true, it does not mean that the risks are the same. Over the decades, the United States has funded research to study the long-term health effects of alcohol and tobacco, but not marijuana. Yet many of the most worrisome brain pathologies from drug use are seen in mental health (as opposed to pulmonary disease and cancer from smoking, and gastric and liver disease from alcohol), where marijuana use is associated with, among other conditions, anxiety and psychiatric disorders. Research suggests that early marijuana use is linked to these problems, but their biological underpinnings are a mystery.

The National Survey on Drug Use and Health has repeatedly found that children who began alcohol or marijuana use before age 15 had a fivefold-increased prevalence of substance use disorders later in life. This may be due to effects of early drug use on the trajectory of the brain’s subsequent development, but we don’t know for sure. What is needed are large longitudinal cohort studies to examine whether marijuana use causes changes in brain function and behavior in young people. The Framingham Heart Study, still ongoing after its initiation 65 years ago, revolutionized our understanding of what causes cardiovascular disease, producing completely unanticipated findings that have led to improved health care and public policy.

The U.S. National Institutes of Health should launch a similar long-term study of preadolescent children and follow them through adolescence into young adulthood, when their brains are most plastic, rapidly developing, reorganizing, and forming enduring neural connections and circuits. The rapid growth of brain science in the past two decades has generated new methods to measure the effects of drugs on brain structure and mental processes. With “big brain” research projects now under way in the United States and Europe, including the BRAIN Initiative announced by President Obama in 2013, to deduce how brain function is linked to behavior and disease, the time is right to rigorously pursue a long-term study of drug effects. Without more scientific evidence to inform policies, we are gambling with the health and safety of our youth in making decisions about psychoactive substances such as marijuana when their real risks are unknown.

— Robert L. DuPont and Jeffrey A. Lieberman

* Robert L. DuPont was the first director of the U.S. National Institute on Drug Abuse (1973–1978) and is president of the Institute for Behavior and Health, Rockville, MD.
## Level of Confidence in the Evidence for Adverse Effects of Marijuana on Health and Well-Being

<table>
<thead>
<tr>
<th>Effect</th>
<th>Overall Level of Confidence*</th>
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<tbody>
<tr>
<td>Addiction to marijuana and other substances</td>
<td>High</td>
</tr>
<tr>
<td>Abnormal brain development</td>
<td>Medium</td>
</tr>
<tr>
<td>Progression to use of other drugs</td>
<td>Medium</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Medium</td>
</tr>
<tr>
<td>Depression or anxiety</td>
<td>Medium</td>
</tr>
<tr>
<td>Diminished lifetime achievement</td>
<td>High</td>
</tr>
<tr>
<td>Motor vehicle accidents</td>
<td>High</td>
</tr>
<tr>
<td>Symptoms of chronic bronchitis</td>
<td>High</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Low</td>
</tr>
</tbody>
</table>

clear and consistent associations and dose-response relations were found between the frequency of adolescent cannabis use and all adverse young adult outcomes.

Silins E et al., The Lancet September 2014.
Changes in Marijuana Policy in the USA

1970
States that Legalized Marijuana Use For Medical Purposes Have Significantly Higher Rates Of Marijuana Use and of Marijuana Abuse and Dependence

NESARC: National Epidemiologic Survey on Alcohol and Related Conditions

Marijuana Consumption by American Indians on or Near Reservations

New NIDA Resources

Marijuana Facts for Teens

How can I tell if my child has been using marijuana?
How does marijuana affect driving?
How many people smoke marijuana?
What are the effects of marijuana?
Marijuana: Facts Parents Need to Know

What does marijuana do to the brain?
What about effects on marijuana pregnancy?
What are the long-term effects of marijuana use?
Are there treatments to help marijuana users?