Kim Blake
4/11/19

S.54

REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Marijuana's Effects on Brain Structure and Function: What Do We Know and What Should We Do? A Brief Review and Commentary

Richard D. deShazo, MD, MACP,[a,b,e] Sara B. Parker, BA,[a] Daniel Williams, PhD,[c] John B. Ingram, MD,[b,d] Mahmoud Elsohly, PhD,[f] Kathryn Rodenmeyer, BA,[e] Kyle McCullouch, BBA[a]

[a]Department of Medicine, University of Mississippi Medical Center, Jackson; [b]Department of Pediatrics, University of Mississippi Medical Center, Jackson; [c]Department of Psychiatry, University of Mississippi Medical Center, Jackson; [d]Department of Neurology, University of Mississippi Medical Center, Jackson; [e]Mississippi Public Broadcasting, Jackson; [f]The National Center for Natural Products Research, University of Mississippi, Oxford.

ABSTRACT

The recent US Food and Drug Administration approval of the marijuana constituent cannabidiol as safe and effective for treatment of 2 rare forms of epilepsy has raised hopes that others of the 500 chemicals in marijuana will be found to be therapeutic. However, the long-term consequences of street marijuana use are unclear, and recent studies raise red flags about its effects. Changes in brain maturation and intellectual function, including decreases in intelligence quotient, have been noted in chronic users and appear permanent in early users in most but not all studies. These studies suggest that at a minimum, regular marijuana use should be discouraged in individuals under the age of 21.
 • The American Journal of Medicine (2019) 132:281–285

KEYWORDS: Adolescents; Brain development; Marijuana; Teenager

INTRODUCTION

The present epidemic of opioid addiction and the enthusiasm about marijuana use by advocates of its legalization may have diverted attention from its reported adverse health effects. These include clinical studies that demonstrate chronic marijuana use is associated with long-term deleterious effects on cognition.[1] Neuroscientists have been carefully pairing neurodiagnostic tools with newer neuroimaging technologies to understand the relationships between the human brain endocannabinoid system and the effects on the system by exogenous cannabinoids, including the major psychoactive cannabinoid from marijuana, tetrahydrocannabinol (THC). Meta-analyses support observations that when compared with nonusers, regular users of marijuana have diminished executive function, attention, learning, memory, and motor skills that persist for varying times after abstinence occurs.[2,3] Combined structural and functional imaging show that morphological brain alterations in the medial temporal and frontal cortex and cerebellum are likely related to the degree of cannabis use. Even more troubling data suggest that when marijuana use begins prior to completion of brain maturation, changes in brain structure and function may persist. If substantiated, these findings have major medical and social implications.

MARIJUANA USE AND EFFECTS ON BRAIN MATURATION, STRUCTURE, AND FUNCTION

Marijuana use starts early in Americans and is the most commonly used illicit drug in Americans 12 years of age and older.[4,5] Seven percent of 8th graders, 15% of 10th graders, and 21% of 12th graders report the use of marijuana in the last month.[6] Of adolescent users, 2.7% meet

Funding: The Selby and Richard McRae Foundation.
Conflict of Interest: None.
Authorship: All co-authors in this paper had access to and played significant roles in the writing of this paper, which is not under consideration by another journal.

Requests for reprints should be addressed to Richard D. deShazo, MD, Department of Medicine, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216.
E-mail address: rdeshazo@umc.edu

0002-9343/© 2018 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.amjmed.2018.09.006

criteria for addiction (cannabis use disorder), as compared with 4.9% of young adult users. Lifetime marijuana use reported in 2016 averaged 15% ages 12-17, 52% ages 18-25, 46% ages 26-65, and 22% ages 65 years and older.[7] Few Americans believe that regular cannabis use is harmful to health, and legalization of marijuana in 29 states and the District of Columbia has increased the public's interest in its possible benefits.[8,9]

Regular use of marijuana is associated with a range of behavioral abnormalities.[1,10] Adolescents who use marijuana are twice as likely to smoke more marijuana and become addicted than those who begin smoking cannabis at a later age. The regular use of cannabis is associated with a decline in short-term memory and cognitive function, poor school or work performance, mood disorders, and psychosis.[10,11] Marijuana impairs the operation of airplanes, automobiles, motorcycles, and trains, and its effects appear to be dose-dependent.[12,13] For instance, automobile accidents occur 2-7 times more frequently while using marijuana.[14]

Now there is evidence of permanent neurological changes associated with marijuana use that begins prior to the age of 21.[15-18] Investigators in New Zealand evaluated the association between regular cannabis use, the results of longitudinal neuropsychological testing, and whether or not functional neurologic decline was disproportionately greater in those who began cannabis use as adolescents than in those who begin use as adults.[19] One thousand thirty-seven individuals in a prospective birth cohort were followed from birth to 38 years old. The presence of cannabis use was determined from interviews of the participants at ages 18, 21, 26, 32, and 38 years, and neuropsychological testing was conducted at age 13, prior to cannabis use, and again at age 38 after patterns of cannabis use had been established. Statistical methods corrected for possible confounders. Regular use was associated with decline across all neuropsychological domains as demonstrated by comprehensive neuropsychological testing. Adverse effects on executive function, memory, and verbal deficits were consistent among users across the cohort, but worse in those who began use of cannabis as adolescents when compared with adults, and greater functional decline was associated with more persistent use. Unfortunately, cessation of cannabis use did not fully restore the diminished neuropsychological functioning present in those who began use prior to age 21. Those findings persisted thereafter, with an average 6-point decrease in intelligence quotient from childhood to adulthood as compared with nonusers. The authors concluded that there is a "neurotoxic effect of cannabis on the adolescent brain" that demonstrates "the importance of prevention and policy efforts targeting adolescent use of marijuana."[19]

CLINICAL SIGNIFICANCE

- Chronic marijuana use is associated with abnormalities in mood and cognition.
- Abnormalities in brain maturation in the areas of the brain that subserve mood and cognitive function are present on functional brain imaging in chronic users.
- There appears to be a dose-response relationship between these abnormalities and the regularity of marijuana use.
- In contrast to adults, abnormalities in cognition associated with chronic marijuana use under age 21 do not resolve with abstinence.
- Individuals under 21 years of age should consider avoidance of marijuana.

A probable explanation for these neuropsychological findings exists in the biology of brain development. Neuroimaging and neurodiagnostic testing performed in tandem show that brain maturation persists throughout the adolescent and young adult years.[20] Gray matter normally decreases in volume during brain maturation due to neuronal pruning, and white matter increases with myelination. Less frequently used neurons are pruned in the preteen years in order to build complex networks for the decision-making of adulthood. The limbic system below and posterior to the cortex matures prior to the gray matter of the prefrontal cortex that is responsible for logical thought and impulse regulation. This appears to explain problems with control of emotion-linked decision-making, risk-taking, and experimentation associated with immaturity.[21,22] Increased myelination in the brain may be visualized and quantitated on brain imaging as an increased volume of "white matter."[23] Myelin-coated nerve fibers distributed within the inner components of the brain facilitate rapid conduction of neuronal electrical potentials and thus, communication among regions of the cerebral cortex and between the brain and structures below it, including the midbrain and spinal cord. These cortico-cortical and cortico-subcortical pathways facilitate cognitive and motor functions.

Structural differences are present in the brains of adolescents who are chronic marijuana users when compared with nonusers.[24] White matter, gray matter, the limbic system, and the cerebellum all showed abnormalities with cannabis use. These findings were summarized as, "Cannabis users show thicker cortices in the left entorhinal cortex and thinner temporal lobes and frontal cortex-volume changes in the cortex, prefrontal cortex, parietal cortex, amygdala, and hippocampus." These same cannabis users performed less well "in tasks requiring attention, memory, processing speed, visuospatial functioning, and executive function."[24] Thus, the abnormalities noted in neuropsychological testing in adolescents who regularly smoke marijuana appear to correlate with abnormalities in functional brain imaging in areas of the brain normally facilitating them. These findings are also present in animal models of chronic cannabis exposure where changes in both brain structure and function are present and correlate with age and duration of exposure.[25]

INCREASING POTENCY OF STREET AND SYNTHETIC MARIJUANA

Over 120 of the 500 chemicals in marijuana are psychoactive compounds, termed cannabinoids.[26,27] The National Center for Natural Products at the University of Mississippi campus in Oxford, Mississippi provides standardized plant marijuana for research and assays for THC content of street marijuana to the US government. Studies there show that marijuana growers have produced marijuana with increasing concentrations of cannabinoids that are rapidly absorbed.[28] *Street marijuana* now exceeds 10% THC on average, but illicit extracts of cannabis like *hash oil* have much higher THC content and *cannabis concentrated extracts* may contain up to 80% THC. *Hashish*, a paste made from cannabis flowers contains about 4 times the content of THC in street marijuana. With combustion, the chemicals in cannabis undergo pyrolysis and hundreds of new chemicals are generated.[26] The vaping of marijuana oil or waxes using e-cigarettes and other devices results in inhalation of even higher concentrations of cannabinoids than produced by smoking. Urine assays for the THC become positive and mild impairments on tests of motor function occur in nonsmokers confined to areas of marijuana smoking, a daunting problem in pregnant females and families with children.[29]

THC binds to, and is a partial agonist of, both CB1 and CB2 cannabinoid receptors. The CB1 cannabinoid receptors are localized in the cortex, motor system, limbic system, and hippocampus are active in the "brain reward system," also known as the "dopaminergic mesolimbic brain circuit," and enhance the release of presynaptic dopamine. This circuit appears to mediate the pleasant effects of drugs of abuse. Chronic use of marijuana downregulates CB1 receptors, requiring higher doses for effect, and abstinence from chronic use leads to CB1 receptor upregulation and withdrawal symptoms.[30]

Marijuana users experience "mild euphoria, relaxation, and perceptual alterations, including time distortion, and intensification of ordinary experiences such as hunger, eating, and listening to music."[31] Some also experience dysphoria, anxiety, or paranoia, especially with synthetic cannabinoids like *herbal incense* and *spice* and synthetic cathinones like *bath salts*. They are direct agonists with a high affinity for the CB1 receptor, probably explaining their extreme toxicity.

The human brain produces endogenous brain endocannabinoids that modulate pain through interaction with its cannabinoid receptors at sites receiving impulses from peripheral sensory nerve endings. They have analgesic effects as well as effects on appetite, nausea, behavior, and memory. Most available information about mammalian endocannabinoids comes from animal studies.[25,32]

IS THERE SPECIAL NEED FOR MARIJUANA AVOIDANCE EFFORTS?

Meier and colleagues[19] have concluded that "Increasing efforts should be directed toward delaying the onset of cannabis use by young people, particularly given the recent trend of younger ages of cannabis-use initiation in the United States. Although there are potential pitfalls in any complex research, their findings are supported by other clinical[33-36] and basic studies.[37,38] Two twin studies of marijuana use were unable to confirm adverse effects of marijuana use on intelligence.[39,40] Marijuana use in adolescents has been associated with not only cognitive effects, but with an increased incidence of psychosis that persists into adulthood and an increased risk of clinical depression after the age of 17.[11,41]

WHAT NEXT?

With this information in mind, what should be done? The National Institutes of Health has funded the Adolescent Brain Cognitive Development (ABCD) Study and awarded 13 grants to perform a prospective 10-year longitudinal evaluation of 10,000 9—10-year-olds in the US. Data to be collected include psychometric and psychosocial assessments, brain imaging and academic performance, genetic testing, and substance use data.[42,43] When completed, data will become available on the effects of marijuana and other substance use in a cohort of users and nonusers large enough to address possible pitfalls in smaller studies. This is important as, contrary to findings in youth, 2 systematic reviews on the effects of marijuana on cognition in adult users suggest that there is at least some recovery of cognitive defects after cessation of chronic marijuana use.[44,45] Delayed effects of marijuana, to include dementia syndromes in adults, have not been reported.

Until more data on the adverse effects of chronic marijuana use are available, the information here supports advocacy by physicians against regular marijuana use in individuals younger than 21. How to go about such advocacy is a conundrum. There is a developing consensus among physician groups that screening individuals as an index to detect marijuana use and some form of intervention is optimal. Because many young people regularly see physicians, physician-initiated screenings could provide the opportunity for information sharing about marijuana use and referral to mental health professionals for therapy of cannabis use disorder. Rate-limiting steps in accomplishing these recommendations include parental consent for younger patients, confidentiality and ethical considerations, the availability of in-clinic resources to perform screenings and substance abuse education, reimbursement for services, and the limited availability of referral sources for mental health consultation and treatment. Moreover, there are inadequate data to define who should be referred or the effectiveness of referral and treatment in young people.

A structured, evidence-based patient screen for substance use is available as the "Screening Brief Intervention and Referral to Treatment" (SBIRT).[46] A SBIRT adaptation for adolescents has been endorsed by the American Academy of Pediatrics, the National Institute on Drug Abuse, and the American Medical Association, among many others. The screen includes questions on alcohol and drug use and the option for a brief intervention based on Motivational Interviewing. Adaptations incorporate nonphysician caregivers into the assessment process, and software embedded into ambulatory clinic registration.

What about drug testing? Many school athletic programs now require parental permission for drug screening as a prerequisite for participation in sports, as do many employers in adult work environments. Drug testing could be considered a voluntary component of routine preventive health evaluations for students from middle school forward or as part of the state driver's licensure process. What to do for those who test positive is unclear.

A rate-limiting factor in basic and clinical research with cannabis is the ability to obtain approval for use of standardized marijuana under protocol for research. Some solution to the problem of access to marijuana for scientific research is overdue.[47]

References

1. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med.* 2014;370(23):2219–2227.
2. Grant I, Gonzalez R, Carey CL, Natarajan L, Wolfson T. Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. *J Int Neuropsychol Soc.* 2003;9(5):679–689.
3. Shreiner AM, Dunn ME. Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: a meta-analysis. *Exp Clin Psychopharmacol.* 2012;20:420–429.
4. United Nations' Office on Drugs and Crime, World Drug Report, Vienna 2016. Available at: https://www.unodc.org/doc/wdr2016/WORLD_DRUG_REPORT_2016_web.pdf. Accessed September 5, 2018.
5. Center for Behavioral Health Statistics and Quality (2015). Behavioral health trends in the United States: results of the 2014 National Survey on Drug Use and Health. Available at: https://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf.Accessed September 5, 2018.
6. National Institute on Drug Abuse: Advancing Addiction Science. Monitoring the Future survey: high school and youth trends. Available at: www.drugabuse.gov/publications/drugfacts/high-school-youth-trends. Accessed September 5, 2018.
7. Substance Abuse and Mental Health Administration. Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2015 and 2016. Available at: https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.htm. Accessed September 5, 2018.
8. Weir K. Marijuana and the developing brain. *Am Psychol.* 2015;46:48. Available at: http://www.apa.org/monitor/2015/11/marijuana-brain.aspx. Accessed September 5, 2018.
9. Harrison G, Pope Jr HG, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. *JAMA.* 1996;275:521–527.
10. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013. Available at: https://dsm.psychiatryonline.org/doi/full/10.1176/appi.books.9780890425596.dsm16#x29473.2601838. Accessed January 30, 2018.
11. Jensen FE, Nutt AE. The Teenage Brain: A Neuroscientist's Survival Guide to Raising Adolescents and Young Adults. Chapter 9, New York, NY: HarperCollins Publishers; 2015. p. 141–158.
12. Leirer VO, Yesavage JA, Morrow DG. Marijuana carry-over effects on air craft pilot performance. *Aviat Space Environ Med.* 1991;62:221–227.
13. Leggett T. United Nations Office on Drugs and Crime. A review of the world cannabis situation. *Bull Narc.* 2006;58:1–155.
14. Rogeberg O, Elvik R. The effects of cannabis intoxication on motor vehicle collision revisited and revised. *Addiction.* 2016;111:1348–1359.
15. Murray RM, Morrison PD, Henquet C, Di Forti M. Cannabis, the mind and society: the harsh realities. *Nat Rev Neurosci.* 2007;8:885–895.
16. Pope HG Jr, Gruber AJ, Hudson JI, et al. Early-onset cannabis use and cognitive defects: what is the nature of the association? *Drug Alcohol Depend.* 2003;69:303–310.
17. Gruber SA, Sagar KA, Dahlgren MK. Age of onset of marijuana use and executive function. *Psychol Addict Behav.* 2012;26:496–506.
18. Winters KC, Arria AM. Adolescent brain development and drugs. *Prev Res.* 2011;18:21–24.
19. Meier MH, Caspi A, Ambler A, et al. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci U S A.* 2012;109:E2657–E2664.
20. Giedd JN. Structural magnetic resonance imaging of the adolescent brain. *Ann NY Acad Sci.* 2004;1021:77–85.
21. Gogtay N, Giedd JN, Lusk L, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A.* 2004;101:8174–8179.
22. Squeglia LM, Jacobus J, Tapert SF. The influence of substance use on adolescent brain development. *Clin EEG Neurosci.* 2009;40:31–38.
23. Ladouceur CD, Peper JS, Crone EA, Dahl RE. White matter development in adolescence: the influence of puberty and implications for affective disorders. *Dev Cogn Neurosci.* 2012;2:36–54.
24. Meruelo AD, Castro N, Cota CI, et al. Cannabis and alcohol use, and the developing brain. *Behav Brain Res.* 2017;325:44–50.
25. Jager G, Ramsey NF. Long-term consequences of adolescent cannabis exposure on the development of cognition, brain structure and function: an overview of animal and human research. *Curr Drug Abuse Rev.* 2008;1:114–123.
26. ElSohly HN, ElSohly MA. Marijuana smoke condensate: chemistry and pharmacology. In: ElSohly MA, ed. *Marijuana and Cannabinoids,* New York, NY: Humana Press; 2007:67–97.
27. Atakan Z. Cannabis, a complex plant: different compounds and different effect on individuals. *Ther Adv Psychopharmacol.* 2012;2:241–254.
28. Elsohly MA, Mehmedic Z, Foster S, et al. Changes in cannabis potency over the last 2 decades (1995-2014): analysis of current data in the United States. *Biol Psychiatry.* 2016;79:613–619.
29. National Institute on Drug Abuse. Marijuana. Available at: https://www.drugabuse.gov/publications/research-reports/marijuana/what-are-effects-secondhand-exposure-to-marijuana-smoke. Accessed September 5, 2018.
30. Herkenham M, Lynn AB, Little MD, et al. Cannabinoid receptor location in the brain. *Proc Natl Acad Sci U S A.* 1990;87:1932–1936.
31. Hall W, Degenhardt L. Adverse effects of non-medical cannabis use. *Lancet.* 2009;372:1383–1391.
32. Manzaneres J, Julian MD, Carrascosa A. Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes. *Curr Neuropharmacol.* 2006;4:239–257.
33. Schweinsburg AD, Brown SA, Tapert SF. The influence of marijuana use on neurocongnitive functioning in adolescents. *Curr Drug Abuse Rev.* 2008;1:99–111.
34. Pope Jr HG, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. *JAMA.* 1996;275:521–527.
35. Solowij N, Stephens RS, Roffman RA, et al. Cognitive functioning of long-term heavy cannabis users seeking treatment. *JAMA.* 2002;287(9):1123–1131.
36. Camchong J, Lim KO, Kumra S. Adverse effects of cannabis on adolescent brain development: a longitudinal study. *Cerebral Cortex.* 2017;27:1922–1930.

37. Mizrahi R, Watts JJ, Tseng KY. Mechanisms contributing to cognitive deficits in cannabis users. *Neuropharmacology*. 2017;124:84–88.
38. Lawston J, Borella A, Robinson JK, Whitaker-Azmitia PM. Changes in hippocampal morphology following chronic treatment with the synthetic cannabinoid WIN 55,212-2. 2000. *Brain Res*. 2000;877 (2):407–410.
39. Lyons MJ, Bar JL, Panizzon MS, et al. Neuropsychological consequences of regular marijuana use: A twin study. *Psychol Med*. 2004;34(7):1239–1250.
40. Jackson NJ, Isen JD, Khoddam R, et al. Impact of adolescent marijuana use on intelligence: results from two longitudinal twin studies. *Proc Natl Acad Sci U S A*. 2016;113(5):E500–E508. Available at: http://www.pnas.org/content/113/5/E500. Accessed September 5, 2018.
41. Kuepper R, van Os J, Lieb R, Wittchen HU, Höfler M, Henquet C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. *BMJ*. 2016;342: d738.
42. Collaborative Research on Addiction at NIH. Adolescent Brain Cognitive Development Study. Available at: https://addictionresearch.nih.gov/abcd-study. Accessed September 5, 2018.
43. Adolescent Brain Cognitive Development. Teen brains. Today's Science. *Brighter Future*. Available at: https://abcdstudy.org/about.html. Accessed September 5, 2018.
44. Broyd SJ, Van Hell HH, Beale C, Yücel M, Solowij N. Acute and chronic effects of cannabinoids on human cognition-a systematic review. *Biol Psychiatry*. 2016;79:557–567.
45. Nader DA, Sanchez ZM. Effects of regular cannabis use on neurocognition, brain structure and function: a systematic review of findings in adults. *Am J Drug Alcohol Abuse*. 2017;12:1–15.
46. Substance Abuse and Mental Health Services Administration. Screening, Brief Intervention, and Referral to Treatment (SBIRT). Available at: https://www.samhsa.gov/sbirt. Accessed September 5, 2018.
47. Bostwick JM. Blurred boundaries: the therapeutics and politics of medical marijuana. *Mayo Clinic Proc*. 2012;87:172–186.