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Marijuana on the Mind? The Impact of Marijuana on Cognition, Brain Structure, and Brain Function, and Related Public Policy Implications

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Abstract

Although marijuana (MJ) has been used for thousands of years, the public's opinion of MJ has shifted drastically over the past century, leaving many wondering about its potential risks and benefits. This article summarizes research detailing the impact of recreational MJ and related variables (frequency, magnitude, potency, and mode of MJ use) on cognition, brain structure, and brain function. MJ use, particularly at young ages, has been reported to undermine cognition, as well as alter brain structure and function. Furthermore, we discuss how data from recreational MJ studies, as well as more recent medical marijuana (MMJ) research findings, relate to legalization efforts. Considerations for policymakers, such as age limits, guidelines for safe use, and the therapeutic potential of certain constituents of MJ (i.e., cannabidiol), are also outlined. In recent years, policy has outpaced science; important areas in need of further research are noted.

Keywords

marijuana, cognition, brain structure, brain function, cannabinoids, CBD, THC, medical, recreational, policy

Tweet

An overview of recreational marijuana's impact on the brain, noting issues for consumers and policymakers to consider including medical MJ.

Key Points

- Recreational marijuana (MJ) use relates to poorer cognition across numerous domains (particularly executive function and memory), as well as alterations in brain structure and function.
- Earlier age of MJ onset (i.e., during adolescence), as well as higher frequency and magnitude of use, relate to further impairment.
- Medical MJ (MMJ) may confer a unique impact on the brain, given that MMJ consumers are often adults who are beyond critical neurodevelopmental periods and who may also seek products based on therapeutic potential, rather than for mood altering effects.
- Safe guidelines for frequency and magnitude of use, MJ potency, and use of concentrates are critical considerations for policymakers; however, further research is needed to facilitate informed decision making.

Introduction

Marijuana (MJ) has been used for thousands of years. Although referenced in Chinese medicine as early as 2700 BC, it was not until 1850 that MJ was added to the U.S. pharmacopeia and considered part of mainstream medicine in the Western world. In the early 1900s, recreational use of MJ emerged in the United States, but as prohibition sentiments grew, many states also began banning cannabis. The political climate continued to strongly influence the public's view of MJ, eventually leading to its removal from the U.S. pharmacopeia in 1942, marking one of several pivotal shifts in the nation's view toward cannabis. In 1970, the Controlled Substances Act declared MJ a Schedule I substance, which by classification deems it as having "no currently accepted medical use, no demonstrated safety profile and a high potential for abuse" and considers it a danger

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due to "potentially severe psychological or physical dependence" (DEA.gov, n.d.).

However, in subsequent years, several states voted to decriminalize MJ; in 1996, California became the first to approve medical marijuana (MMJ). Since then, MJ continues to make headlines as an increasing number of states have followed suit. To date, 28 states and Washington, D.C., have enacted full MMJ programs, whereas 17 states allow limited access to specific MMJ products. Eight states and Washington, D.C., have also legalized recreational MJ use. Legal MJ is considered the fastest growing market in the United States, with a current estimated value of US$6.7 billion, which could reach US$21.8 billion by 2020 (Arcview Market Research, 2016).

Currently, 22.2 million Americans report past-month MJ use (Center for Behavioral Health Statistics and Quality, 2015), and given the trajectory of MJ legalization, perceived risk and harm related to MJ use is at an all-time low. In 2015, fewer than half of high school seniors thought regular MJ smoking was harmful, a significant drop from previous years (Johnston et al., 2015). In fact, more high school seniors report using MJ daily (6%) than smoking cigarettes daily (5.5%), and more than 21% of seniors report current MJ use. As adolescence is a time of neuromaturation, and increasing evidence demonstrates that the adolescent brain is more vulnerable to the effects of drugs than the adult brain, those at the greatest risk of adverse consequences represent a growing population of MJ consumers, a combination that poses public health concerns (Schneider, 2008).

During adolescence, brain regions, particularly those associated with executive functioning (e.g., problem solving, planning, inhibition), undergo processes that refine and strengthen neural networks; this occurs until at least the mid-20s. Throughout emerging adulthood, white matter (WM) volume and integrity also increase, which relates to improvements in neural conductivity (Giedd et al., 1999; Jernigan & Gamst, 2005). Given these critical neurodevelopmental changes, the brains of teens and emerging adults are particularly vulnerable to the effects of drugs, compared with adults who are developmentally mature.

MJ interacts with the body's natural endocannabinoid (eCB) system, which includes two types of cannabinoid receptors, CB1 and CB2 (although some have posited a third receptor type), and the body's own endogenous cannabinoids, including anandamide and 2-arachidonoyl glycerol (2-AG). The eCBs (those that naturally occur in the body) and exogenous cannabinoids (those that are not produced by the body) act primarily via CB1 receptors, predominantly distributed in the central nervous system, and CB2 receptors, located in both the central nervous system and peripheral organs. The eCB system plays a significant role in homeostasis and neuroplasticity, including neurogenesis and refinement of neuronal connections (Befort, 2015; Egerton, Allison, Brett, & Pratt, 2006; Katona & Freund, 2008). Increased eCB signaling is associated with improved cognition (Egerton et al., 2006), reduced stress response, emotional regulation, and increased endogenous reward signaling (Befort, 2015; Hill & McEwen, 2010).

Delta-9-tetrahydrocannabinol (THC), the primary psychoactive constituent of MJ, is a CB1 agonist with strong binding affinity for CB1 receptors, meaning that THC efficiently activates CB1 receptors. Given that the eCB system affects growth, differentiation, positioning, and connectivity among neurons, exposure to exogenous (external) cannabinoids such as THC may disrupt such neural development, especially during adolescence.

However, it is of note that preliminary evidence also suggests that MJ and its constituents also likely hold extraordinary potential for the treatment of a number of medical conditions (Whiting et al., 2015). Unfortunately, as a result of MJ's classification as a Schedule I substance, relatively few trials have been conducted regarding the effects of MMJ. Despite the paucity of MMJ data, decades of research have explored the effects of recreational MJ use on the brain. This article reviews salient findings regarding the impact of recreational MJ on cognition, brain function, and brain structure, and discusses future directions for MJ research as it pertains to public policy and MMJ programs.

Neurocognitive Consequences of MJ Use

Cognition

In recent years, numerous studies have examined the cognitive consequences of MJ use. Overall, the majority of studies assessing the chronic effects of MJ have shown that those who use MJ regularly exhibit poorer cognitive performance across a range of domains, relative to non-MJ users. Although the findings summarized below are not exhaustive, taken together, recent reviews of the effects of MJ suggest that executive functioning and memory are most strongly affected by regular MJ use. Although processing speed is also adversely impacted, findings are more inconsistent with regard to IQ.

Executive function (EF). EF is a multi-faceted cognitive construct, which involves controlling and enacting behaviors to attain a goal, and includes processes such as planning, reasoning, inhibitory processing, self-monitoring, and problem solving. Although studies of EF often examine a variety of specific skills within this domain (e.g., attention, decision making, risk taking, inhibition, and verbal fluency), among cross-sectional studies, there is general consensus that MJ use negatively impacts EF (for review, see Crean, Crane, & Mason, 2011). Moreover, those with an earlier age of MJ onset and higher levels of MJ use appear more impaired than later onset users on EF measures (Gruber, Sagar, Dahlgren, Racine, & Lukas, 2012; Sagar et al., 2015). Several investigations have also noted that lower EF appears to predict

increased MJ use (Dahlgren, Sagar, Racine, Dreman, & Gruber, 2016; Squeglia, Jacobus, Nguyen-Louie, & Tapert, 2014) and MJ-related problems (Day, Metrik, Spillane, & Kahler, 2013).

Memory. Cross-sectional studies also demonstrate that MJ use adversely affects numerous aspects of memory (for review, see Broyd, van Hell, Beale, Yücel, & Solowij, 2016; Solowij & Battisti, 2008). In particular, studies have consistently documented impaired verbal learning and memory in heavy MJ users. Adolescent MJ users exhibited similar verbal learning deficits as adults, long-term heavy MJ users, despite less cumulative exposure (Solowij et al., 2011), providing evidence that the developing brain may be particularly vulnerable. In addition, adolescent MJ users have demonstrated poorer story memory, relative to age-matched control participants (Medina et al., 2007).

Despite strong evidence for verbal memory impairment, findings in other areas of memory function, namely, associative memory and visuospatial memory, are less robust. For example, although Sneider, Gruber, Rogowska, Silveri, and Yurgelun-Todd (2013) reported deficits in visual memory retrieval in MJ users, Smith, Longo, Fried, Hogan, and Cameron (2010) did not detect performance deficits on a visual memory task. In addition, although few have utilized associative memory tasks, one recent study failed to detect differences between MJ users and healthy controls (Jager, Block, Luijten, & Ramsey, 2010).

Processing speed. Only a handful of studies have examined processing speed with mixed results. Although Becker, Collins, and Luciana (2014) observed better processing speed in college-aged MJ smokers, most have observed deficits in current (Auer et al., 2016) and recent MJ users (Thames, Arbid, & Sayegh, 2014) relative to non-users, including a longitudinal study (Fried, Watkinson, & Gray, 2005). Furthermore, some evidence suggests that increased use (Lisdahl & Price, 2012) and higher cumulative exposure (Auer et al., 2016) to MJ are related to slower psychomotor/processing speed.

IQ. Until recently, most longitudinal studies reported lower IQ among MJ users relative to healthy controls (e.g., Fried et al., 2005; Meier et al., 2012). However, two recent longitudinal studies with the largest sample sizes to date have challenged these findings. In two sets of adolescent twins assessed initially during adolescence and again during emerging adulthood, although MJ users demonstrated lower IQ relative to non-users, MJ-using twins failed to show significantly greater IQ decline relative to their abstinent siblings (Jackson et al., 2016). Accordingly, findings suggest that the observed declines in IQ might not be a direct result of MJ exposure but rather attributable to familial factors. Similarly, a second longitudinal study found that after adjusting for confounding variables, MJ users did not display declines in IQ or exhibit lower educational attainment relative to never-users (Mokrysz et al., 2016). Given inconsistent findings, the impact of MJ on IQ remains an area for further exploration.

Brain Structure

Advanced neuroimaging techniques provide the opportunity to examine the impact of MJ on several aspects of brain structure, including gray matter (GM) and WM. GM is comprised of neuronal cell bodies and is responsible for information processing and decision making. A recent review of 23 neuroimaging studies (Lorenzetti, Solowij, & Yücel, 2016) reported that regular MJ users consistently exhibit reductions in GM volume across brain regions, particularly in the hippocampus. In contrast, MJ users generally have larger cerebellar and striatal volumes. These somewhat mixed findings are consistent with a previous review in which authors reported bidirectional structural imaging findings, dependent on the brain region under investigation (Batalla et al., 2013). However, in general, regions commonly altered in MJ users are typically those with high densities of CB1 receptors (Lorenzetti et al., 2016). Furthermore, several studies link GM alterations to increased executive dysfunction (Medina et al., 2009, Medina, Nagel, & Tapert, 2010; Price et al., 2015), impulsivity (Churchwell, Lopez-Larson, & Yurgelun-Todd, 2010), and poorer verbal memory (Ashtari et al., 2011), suggesting that structural alterations negatively impact cognition.

Alterations also appear to be influenced by age of onset and increased MJ use. For example, Filbey, McQueeny, DeWitt, and Mishra (2015) found opposing effects on cortical thickness in early (thickening) versus late (thinning) onset users. In addition, although a recent 3-year longitudinal study of young adult, heavy MJ users observed no effect on GM at follow-up, cross-sectional analyses at baseline indicated that higher MJ use was related to decreased GM volume in the medial temporal lobe, including the hippocampus (Koenders et al., 2016). The authors concluded that although adolescent MJ users are vulnerable to GM reductions, little further damage appears to occur after early adulthood.

Whereas GM is responsible for decision making, WM plays a critical role in promoting efficient communication both within and between brain regions. In general, studies link MJ use to reduced WM integrity in several areas of the brain (prefrontal, limbic, parietal, and cerebellar tracts) in adolescent and emerging adult MJ users (e.g., Clark, Chung, Thatcher, Pajtek, & Long, 2012; Epstein & Kumra, 2015; Gruber, Silveri, Dahlgren, & Yurgelun-Todd, 2011; Gruber, Dahlgren, Sagar, Gonenc, & Lukas, 2014). In a large sample of MJ users ($n = 466$), earlier age of MJ onset was related to lower WM coherence (Orr, Paschall, & Banich, 2016). Conversely, slightly higher coherence has also been observed in adolescent MJ users in certain regions (DeLisi et al., 2006)

or at certain stages of development (Jakabek, Yücel, Lorenzetti, & Solowij, 2016), suggesting that although MJ affects multiple WM tracts, directionality remains somewhat unclear. Lower WM integrity also correlates with higher impulsivity scores, specifically in early onset MJ users (Gruber et al., 2014). Alterations in WM have been identified as a potential risk factor for poorer EF and symptoms of cannabis-use disorders (Clark et al., 2012). Overall, studies suggest that MJ-related alterations in WM integrity are complex and are likely related to specific neurodevelopmental stages (Becker, Collins, Lim, Muetzel, & Luciana, 2015; Jacobus, Squeglia, Bava, & Tapert, 2013; Jakabek et al., 2016). Nonetheless, WM alterations appear to be related to negative outcomes.

Brain Function

Functional magnetic resonance imaging (fMRI) provides information about brain activity, often during the completion of cognitive tasks. Several fMRI review papers have found strong evidence that MJ use is related to altered activation patterns (Batalla et al., 2013; Jacobus & Tapert, 2014; Lisdahl, Gilbart, Wright, & Shollenbarger, 2013). During tasks involving frontal/EF, attention, spatial/verbal working memory, verbal learning, affective processing, and reward processing, MJ users exhibit altered activation in the prefrontal cortex (PFC) and orbitofrontal, cingulate, parietal, insular, subcortical/limbic, and cerebellar regions (Lisdahl, Wright, Kirchner-Medina, Maple, & Shollenbarger, 2014, for review), compared with non-using control subjects. Similar to studies of cognition and brain structure, fMRI studies have also revealed that earlier onset of use and longer duration of use relate to altered activation during cognitive tasks requiring decision making (Behan et al., 2014; Sagar et al., 2015; Vaidya et al., 2012) and inhibition (Gruber, Dahlgren, Sagar, Gönenc, & Killgore, 2012; Tapert et al., 2007).

Additional Factors Affecting the Impact of MJ Use

Age of Onset, Frequency, and Magnitude of Use

As noted, MJ use during adolescence appears to result in negative consequences. Furthermore, earlier age of MJ onset may be inextricably linked to higher frequency and magnitude (grams used) of MJ use. In recent work demonstrating that age of onset predicts cognitive impairment, both frequency and magnitude of MJ use also predict impairment (Sagar et al., 2015). In fact, MJ users with early onset (prior to age 16) reportedly use MJ nearly twice as often and more than 2.5 times as much relative to late-onset users (Gruber, Sagar, et al., 2012; Sagar et al., 2015). Overall, frequency and duration of use appear to be key factors in determining the extent of MJ-related impairment (Lisdahl & Price, 2012; Solowij et al., 2012; Thames et al., 2014).

The Role of Abstinence

Abstinence also influences MJ's effects on cognition; however, few studies have specifically examined the differential impact of variable lengths of abstinence, which may account for heterogeneity of findings. Emerging evidence suggests recovery of cognitive function after relatively brief abstinence periods (Hanson et al., 2010; Medina et al., 2007). In one study, adolescent MJ users who abstained for at least 3 months demonstrated similar cognitive performance relative to healthy controls (Fried et al., 2005). Thus far, however, few have examined the impact of *extended* abstinence periods on cognition, brain structure, and brain function. In short, although preliminary evidence suggests some "normalization" after cessation of use, additional research is needed in this area.

Gender

Data suggest that MJ-related cognitive decrements may manifest differently in males and females (Crane, Schuster, & Gonzalez, 2013). For example, Crane, Schuster, Mermelstein, and Gonzalez (2015) reported that earlier age of onset was related to poorer episodic memory in female but not male MJ users. In males, however, increased MJ use was associated with poorer performance on a decision-making task. Lisdahl and Price (2012) found that although MJ use was associated with poorer psychomotor speed, cognitive slowing was more prominent in males. Similarly, neuroimaging studies have revealed gender differences among MJ users (McQueeny et al., 2011; Medina et al., 2009). Additional research needs to explore the unique impact of MJ in males versus females.

Marijuana Constituents: "Not All Marijuana Is the Same"

"Marijuana" typically describes all constituents derived from the plant *Cannabis Sativa L*. There are two main species of MJ, sativa and indica, and countless strains are hybrids of these species. Cannabis contains more than 100 phytocannabinoids and many have unique effects. However, THC is most commonly studied due to its role as the primary psychoactive constituent of MJ. Research has shown that the potency of recreational MJ (measured as THC concentration) has increased exponentially over the last two decades. From 1995 to 2012, average THC levels in MJ rose from 4% to 12%—an increase of nearly 200% (ElSohly et al., 2016). Furthermore, use of MJ concentrates is becoming increasingly popular. Concentrated products, including "dabs" (the colloquial name for concentrated hash oil created by

extracting THC from flower-based MJ products), shatter, wax, budder, and others all have significantly higher potency relative to traditional flower products, often exceeding 60% THC. Furthermore, these products may also contain residual amounts of solvents (i.e., butane, hexane), often used to make concentrates, which are potentially toxic. To date, little attention has focused on the impact of higher THC-containing products on cognitive performance or measures of brain structure and function in humans. This raises concern that adverse consequences associated with MJ use may be worse now than in the past, particularly among young users.

In contrast, cannabidiol (CBD), the primary non-psychoactive constituent of MJ, has become well known for its role in treating intractable pediatric epilepsy, and has demonstrated promise in treating other medical conditions including pain and multiple sclerosis (Giacoppo et al., 2015), as well as psychiatric conditions including anxiety (Blessing, Steenkamp, Manzanares, & Marmar, 2015) and psychosis (Leweke et al., 2012; Zuardi et al., 2009). Unlike THC, CBD has low affinity to both CB1 and CB2 receptors (Izzo et al., 2009), and has been shown to mitigate some of the negative effects of THC, including structural alterations in the brain (Lorenzetti et al., 2016; Yücel et al., 2016) and adverse psychological symptoms (Morgan et al., 2012). Although some studies have also begun to investigate the therapeutic and protective properties of other cannabinoids, such as cannabigerol (CBG), cannabichromene (CBC), and cannabinol (CBN), more thorough research is needed.

Discussion

Marijuana and Public Policy

More than ever before, the nation is anxious to understand the impact of MJ use, as states continue to ease restrictions on medical and recreational use. Studies of recreational MJ use provide evidence that MJ adversely affects the brain, particularly in adolescents or those with earlier onset of use. Adolescence is a period of neurodevelopmental vulnerability and, as with other drugs, exposure to MJ is more likely to result in alterations than in a mature system. Policymakers should carefully consider age restrictions, based on scientific evidence highlighting the developmental trajectory of the adolescent brain. MJ products must not target youth in advertisements, and safe guidelines for packaging MJ products must be established, as accidental ingestion of edibles by children is a primary concern in states with legalized MJ.

Studies also indicate that increased patterns of MJ use, which appear to be closely tied to earlier onset of MJ of use, are related to greater impairment and increased neural alterations. Accordingly, policymakers are encouraged to engage in dialogue regarding safe limits of MJ use, especially as limited research is currently available. Additional studies of light or casual MJ users are necessary. A further consideration regarding safety is the method of administration or "mode" of use. Although smoking MJ is traditional among recreational users, other modes have increased in popularity, including vaporizing, "dabbing," and using edibles, tinctures, and oils. Research should help determine whether different modes of use have unique effects, and whether some are safer than others in terms of required accessories, ability to regulate dose, and medical or psychological side effects.

In addition, as MJ plants and related products are highly variable with regard to their cannabinoid profiles, policy is likely better suited if it takes into account the effects of specific constituents of the plant rather than treating all "marijuana" as the same. However, this should not be interpreted to mean that cannabinoids should only be isolated for use; data suggest that products derived from whole-plant extractions are more efficacious than isolated compounds (Gallily, Yekhtin, & Hanus, 2015; Grinspoon & Bakalar, 1997). Instead, limits on THC potency as well as minimums for constituents with potentially beneficial effects, such as CBD, could be considered, especially in light of rising levels of THC coupled with decreasing CBD. As THC is correlated with the negative effects observed in recreational users, and CBD has neuroprotective properties, reversing this trend could be an important next step in public policy.

Research focused on the impact of MMJ is also critical, as the number of individuals certified for MMJ use increases. Although studies of recreational MJ are available, the status of MJ as a Schedule I substance has resulted in limited research efforts aimed at assessing the impact of MMJ on various aspects of functioning. These restrictions have created a system in which numerous products available for sale (i.e., non-psychoactive hemp-based products with little to no THC) and taken by countless consumers are not eligible to be studied in clinical trials. Furthermore, although recreational MJ may result in adverse effects on the brain, particularly among adolescents, the impact may be different in adult MMJ patients who are beyond the period of neurodevelopmental vulnerability. MMJ consumers are also more likely to select cannabinoid products for their therapeutic properties rather than high THC potency, which may provide some degree of protection. Furthermore, if physical or psychological symptoms are addressed by MMJ use, overall function may improve. In a recent pilot study assessing the impact of MMJ in certified patients previously naïve to MJ, patients experienced moderate improvement in some aspects of cognitive functioning as well as self-reported ratings of reduced sleep disturbance, decreased symptoms of depression, attenuated impulsivity, and positive changes in quality of life after 3 months of MMJ treatment (Gruber et al., 2016). Consistent with other investigations (Haroutounian et al., 2016), patients also reported reduced use of conventional medications including opiates, which often impair cognitive function and have additional unwanted side effects. These findings call for additional MMJ research, especially in light of the opioid epidemic, which has become a national epidemic in recent years.

Conclusions and Recommendations

As the dialogue regarding legalization of recreational and MMJ continues, perceived risk of MJ use has fallen to an all-time low. Consequently, those with the highest neurodevelopmental vulnerability are using MJ more frequently than in previous years, posing a serious public health issue. A growing body of evidence indicates that relative to non-MJ users, heavy MJ users exhibit poorer performance on cognitive tasks, altered patterns of brain activity, and lower frontal WM coherence, which are highly moderated by age of onset of MJ use. Given the potential therapeutic benefits of MJ, however, it is important to weigh these risks with the benefits. Policy has outpaced science, and eased restrictions allowing citizens to use MJ, in some cases without the benefit of appropriate research. Additional investigation is warranted and necessary to guide informed policy decisions. As states consider legislation for MJ use, it is imperative to determine safe guidelines regarding the impact of MJ on the brain, particularly during critical periods of neurodevelopment. Although "just say no" did not work as a successful prevention policy, "just not yet" may be a more effective and informed message to promote, especially among our nation's youth.

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