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Marijuana Matters: Reviewing the Impact of Marijuana on Cognition, Brain Structure and Function, & Exploring Policy Implications and Barriers to Research

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Abstract

The neurobiologic effects of cannabis, commonly referred to as “marijuana” (MJ), have been studied for decades. The impact of recreational MJ use on cognition and measures of brain function and structure is outlined and variables influencing study results are discussed, including age of the consumer, patterns of MJ use, variations in MJ potency and the presence of additional cannabinoids. Although evidence suggests that chronic, heavy recreational MJ use is related to cognitive decrements and neural changes, particularly when use begins in adolescence, findings from studies of recreational MJ users may not be applicable to medical marijuana (MMJ) patients given differences in demographic variables, product selection, and reasons for use. Although additional research is needed to fully understand the impact of MJ and individual cannabinoids on the brain, current findings are beginning to inform public policy, including considerations for age limits, potential limits for some cannabinoids, and guidelines for use. However, barriers continue to impede researchers’ ability to conduct studies that will guide policy change and provide vital information to consumers and patients regarding best practices and safest methods for use. The need for information is critical, as legalization of MJ for medical and recreational use is increasingly widespread.

Keywords

Marijuana; cannabis; medical marijuana; cognition; neuroimaging; MRI; policy

Introduction

Cannabis has been an integral part of many civilizations, with references in texts of ancient cultures including China, India, and Egypt spanning thousands of years. Cannabis has

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endured a tumultuous history across the globe. In the United States, for example, cannabis was added to the US Pharmacopeia in 1850 and considered mainstream medicine in the western world. By the early 1900s, recreational use of cannabis emerged, but as prohibition sentiments grew, many states began banning cannabis, newly termed ‘marijuana’ (MJ). Over time, a shifting political and social landscape marked in part by the Marihuana Tax Act of 1937 (opposed by the American Medical Association) and the “Reefer Madness” movement ultimately influenced the public’s view. The removal of cannabis from the Pharmacopeia in 1942 further underscored concerns regarding therapeutic use, and in 1970, the newly implemented Controlled Substances Act declared MJ a Schedule I substance, the most restrictive category. Alongside drugs like heroin, Schedule I substances are classified as having no currently accepted medical use, a lack of accepted safety, and a high potential for abuse, and are considered a danger due to “potentially severe psychological or physical dependence” (DEA.gov). In 1996, California became the first state to approve medical marijuana (MMJ), and to date, 30 states and Washington DC have voted to enact comprehensive MMJ programs; 17 states allow limited access to specific MMJ products, leaving only 3 states in the nation without access. In addition, currently 9 states and Washington DC have legalized recreational MJ use for adults, with several other states pending legislation. Considered the fastest growing market in the United States, with a current estimated value of \$9.7 billion, legal MJ sales could reach \$24.5 billion by 2021 (The State of Legal Marijuana Markets: Mid-Year Update, 2017). Around the world, the status of MJ differs from country to country. Many have decriminalized MJ and several others have legalized MJ for medical use, including Israel, Canada, Argentina, Chile, Australia, and others. Interestingly, the Netherlands uses the Opium Act to categorize drugs into two classes; ‘soft,’ which includes cannabis and other substances considered ‘less damaging,’ and ‘hard’ which includes substances like heroin, cocaine, and amphetamines which carry greater risk (“Difference between hard and soft drugs,”). Despite the fact that both classes are illegal, the Netherlands tolerates the use and sale of soft drugs, notably cannabis (in all forms) under certain conditions, specifically in coffee shops, which has historically helped to make Amsterdam a popular tourist destination. Uruguay became the first country to fully legalize MJ for adult consumption in 2013, and Canada appears poised to follow suit in the near future.

The term “marijuana” typically describes *all* constituents derived from the plant *Cannabis Sativa L* which is posited to have two main species, sativa and indica, and countless strains represent hybrids of the two. Historically, sativa and indica have been differentiated by their THC content (Hillig and Mahlberg, 2004); in general indica is thought to contain higher levels of THC, but some sativa strains have also been found to have very high THC content (Hazeekamp and Fishedick, 2012). Anecdotal evidence suggests distinct effects for each subspecies, in which sativa is generally seen as energy-inducing, whereas indica is viewed as having relaxing effects (Hazeekamp and Fishedick, 2012), and some users report a preference for sativa vs. indica based on indications for MMJ use (Pearce, Mitsouras, & Irizarry, 2014). However, it is important to note that few studies have directly examined whether the actual chemical compositions or pharmacodynamics truly differ between these two subspecies or their hybrids.

The cannabis plant contains more than 100 phytocannabinoids that interact 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; (Ryberg et al., 2007), and the body's own endogenous cannabinoids, including anandamide and 2-arachidonoyl glycerol (2-AG). Endocannabinoids (which naturally occur in the body) and exogenous cannabinoids (those which 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 and Freund, 2012). 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 and McEwen, 2010).

Delta-9-tetrahydrocannabinol (THC), the primary psychoactive constituent of MJ, is a CB1 agonist with strong binding affinity for CB1 receptors (Di Marzo and Piscitelli, 2015) and is mainly responsible for the subjective "high" felt by recreational MJ users who often seek strains and products with high concentrations of THC. Given that the eCB system affects growth, differentiation, positioning, and connectivity among neurons, exposure to exogenous cannabinoids such as THC may disrupt such neural development, especially during adolescence. Analyses of recreational MJ products revealed that between 1995 and 2014, levels of THC nearly tripled (ElSohly et al., 2016). In addition, highly potent products termed "concentrates" (i.e., dabs, shatter, wax, budder) have also surged in popularity in recent years, raising additional concerns about the impact of recreational MJ use on the brain. However, evidence also suggests that MJ and its constituents likely hold extraordinary potential for the treatment of a number of medical conditions (Whiting et al., 2015). Cannabidiol (CBD), the primary non-intoxicating constituent of the plant, has become well-known for its role in treating intractable pediatric seizure disorders (Devinsky et al., 2016) 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, Borrelli, Capasso, Di Marzo, & Mechoulam, 2009), and has been shown to mitigate some of the negative effects of THC, including cognitive decrements and adverse psychological symptoms. For example, Morgan and colleagues (2012) found that individuals with high THC levels (as measured by hair samples) exhibited poorer performance on tests of episodic and verbal memory, but those who had detectable amounts of CBD demonstrated better recognition memory. In addition, higher THC levels were correlated with increased symptoms of depression and anxiety, while the presence of CBD was associated with lower scores on scales assessing psychotic-like symptoms. Interestingly, some studies have shown that the presence of CBD may also mitigate structural brain alterations noted in chronic MJ users (Lorenzetti, Solowij, & Yucel, 2016; Yucel et al., 2016). These findings are particularly compelling, as THC levels have continued to rise and CBD levels have declined to nearly undetectable levels in recreational MJ products (ElSohly et al., 2016).

Despite a body of evidence demonstrating structural and functional brain alterations among recreational MJ users, MJ is the most commonly used drug worldwide. According to the United Nations Office on Drugs and Crime (“World Drug Report 2017,” 2017), an estimated 183 million people used MJ, which corresponds to approximately 3.8% of the entire world population. This report also cites the United States as having one of the highest rates of MJ consumption, and national US surveys have found that more than 24 million Americans report past month MJ use (*Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health* 2017). Current deliberations over the legalization of MJ often highlight the potential benefits of MMJ, and with the majority of states legalizing MMJ, it is not surprising that perceived risk related to MJ use is at an all-time low. In fact, the most recent US national survey data indicate that more high school seniors use MJ daily (5.9%) than smoke cigarettes (4.2%), more than 37% of seniors reported past-year MJ use, and only 29% of all seniors surveyed thought regular MJ use was harmful (Miech et al., 2017). Further, almost 9% of the national population aged 12 or older currently use MJ (*Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health* 2017), which is potentially concerning given critical neurodevelopmental changes that take place throughout adolescence. During adolescence, a period often marked by increased risk-taking behaviors including experimentation with substance use, brain regions, particularly those associated with executive functioning (e.g., problem solving, planning, inhibition), undergo processes that refine and strengthen neural networks, which continue until at least the mid-20s (Gogtay et al., 2006; Houston, Herting, & Sowell, 2014). Throughout emerging adulthood, white matter volume and integrity also increase, which are associated with improvements in neural conductivity (Giedd et al., 1999; Jernigan and Gamst, 2005). As adolescence is marked by ongoing neuromaturational processes and there is increasing evidence that the adolescent brain is more vulnerable to the effects of drugs than the adult brain, those at the greatest risk for adverse consequences represent a vast and vulnerable population of MJ consumers, a combination that poses serious public health concerns.

To date, the majority of data regarding the impact of MJ is derived from studies of individuals with chronic, heavy recreational use, as MMJ use has traditionally been far less common. In fact, a recent US study examining national survey data found that only 17% of MJ users reported using for medical purposes (Lin, Ilgen, Jannausch, & Bohnert, 2016). Further, given public health concerns regarding adolescent use, many studies have specifically examined adolescent users or those with adolescent onset of MJ use (Coffey and Patton, 2016; Lisdahl, Gilbert, Wright, & Shollenbarger, 2013; Lisdahl, Wright, Kirchner-Medina, Maple, & Shollenbarger, 2014; Lorenzetti, et al., 2016). Studies of recreational MJ users have yielded a large body of research documenting the neural impact of recreational MJ use on the brain using both neuropsychological assessment and neuroimaging techniques, which clarify the underlying structural and functional alterations associated with recreational MJ use. As there is often heterogeneity across study findings, potential moderating variables must be taken into account given overall implications for public policy and considerations for continued research efforts.

Neurocognitive Impact of Recreational MJ Use

Cognition

Numerous studies have documented the effects of MJ across a wide range of cognitive domains including, but not limited, to various aspects of memory, executive function/working memory, processing speed, and overall intelligence. Among review articles, there is general consensus that MJ particularly impacts memory and executive function adversely, and some evidence also suggests decrements in processing speed (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Ganzer, Broning, Kraft, Sack, & Thomasius, 2016; Gruber and Sagar, 2017; Lisdahl, et al., 2014). It is of note, however, that findings with regard to general intelligence (IQ) remain more contradictory across studies (Jackson et al., 2016; Meier et al., 2012; Mokrysz et al., 2016).

Memory and executive function are broad cognitive domains that encompass a variety of related, yet discrete processes. Memory assessments include both visual and verbal aspects of memory as well as one's ability to learn, encode and recall previously learned information. Executive function is a multi-faceted cognitive construct, which involves controlling and executing behaviors in order to attain a goal, and is comprised of numerous processes such as planning, reasoning, complex attention, inhibitory processing, self-monitoring, and problem solving. With regard to studies of memory function, several reviews indicate that recreational MJ use appears to impact a number of individual aspects of memory (Broyd, van Hell, Beale, Yucel, & Solowij, 2016; Ganzer, et al., 2016; Solowij and Battisti, 2008); however, findings are most robust for measures of verbal learning, where decrements have been observed on measures of encoding, recall, and recognition (Solowij and Battisti, 2008). Despite strong evidence for verbal memory impairment among recreational MJ consumers, findings from other areas of memory function, namely associative and visuospatial memory, are less clear. For example, fewer studies note decrements on assessments of visual short-term memory (Hermann et al., 2007; Sneider, Gruber, Rogowska, Silveri, & Yurgelun-Todd, 2013). Working memory, often also considered a core facet of executive function, reflects temporary storage and manipulation of information for problem-solving or mental operations. Results from investigations examining working memory indicate poorer performance among recreational MJ consumers on some paradigms but not others (for review: (Broyd, et al., 2016). For other aspects of executive function, including response inhibition, planning, and decision-making, recreational MJ use appears to affect both current and recent MJ users (e.g., (Becker, Collins, & Luciana, 2014; Dougherty et al., 2013; Fontes et al., 2011; Hanson, Thayer, & Tapert, 2014; Jacobus, Bava, Cohen-Zion, Mahmood, & Tapert, 2009; Sagar et al., 2015; Solowij et al., 2012; Winward, Hanson, Tapert, & Brown, 2014). Further, several investigations also report an association between executive function and MJ use, with higher levels of use typically related to worse performance (Dahlgren, Sagar, Racine, Dreman, & Gruber, 2016; Squeglia, Jacobus, Nguyen-Louie, & Tapert, 2014) and MJ-related problems (Day, Metrik, Spillane, & Kahler, 2013).

To date, only a small number of studies have examined processing speed, a measure reflecting the time it takes to complete a mental task. Although Becker and colleagues

(2014) observed faster processing speed on one measure in young adult MJ smokers, most have observed deficits in current (Auer et al., 2016; Fried, Watkinson, & Gray, 2005) and recent MJ users (Thames, Arbid, & Sayegh, 2014) relative to non-users. Findings with regard to overall intelligence are largely inconsistent. While some studies have reported lower IQ among recreational MJ users relative to healthy controls (Fried, et al., 2005; Meier, et al., 2012), more recent longitudinal studies with larger sample sizes challenge these findings. In one investigation of twins discordant for MJ use, MJ users demonstrated lower IQ relative to non-users, but MJ-using twins failed to show significantly greater IQ decline relative to their abstinent siblings, leading the authors to conclude that the observed decline in IQ might be attributable to familial factors, rather than a direct result of MJ use (Jackson, et al., 2016). Similarly, Mokrysz and colleagues (2016) did not find IQ differences between MJ users and controls after adjusting for confounding variables in a large-scale, longitudinal study.

Brain Function

With the advent of advanced non-invasive imaging techniques, including functional magnetic resonance imaging (fMRI), investigations have begun to clarify the underlying neural substrates associated with cognitive decrements in MJ users. Using a variety of paradigms, researchers have studied functional correlates of MJ use across cognitive domains. While the direction and magnitude of findings are often variable, overall, MJ use is typically associated with altered patterns of brain activation across multiple brain regions. For example, during tasks of executive function, a number of studies have reported altered activation in the frontal cortex (Gruber and Yurgelun-Todd, 2005; Hatchard, Fried, Hogan, Cameron, & Smith, 2014; Kober, DeVito, DeLeone, Carroll, & Potenza, 2014; Sagar, et al., 2015). Although many have examined verbal memory using traditional neuropsychological measures, the majority of fMRI studies have utilized spatial working memory tasks. Interestingly, MJ users generally demonstrate similar behavioral performance compared to healthy controls on these paradigms, yet neural alterations have been observed across studies (Kanayama, Rogowska, Pope, Gruber, & Yurgelun-Todd, 2004; Padula, Schweinsburg, & Tapert, 2007; Schweinsburg et al., 2008; Smith, Longo, Fried, Hogan, & Cameron, 2010; Sneider, et al., 2013), suggesting that less efficient neural strategies may be used by MJ users in order to achieve the same level of performance as non-users.

Other aspects of cognition proposed to be associated with drug use, including associative memory, error monitoring, and reward processing have also been examined in recreational MJ consumers. Overall, functional correlates of each of these processes appear to be altered in MJ users relative to healthy controls. For example, studies of associative memory have indicated attenuated activation in frontal, temporal, and parahippocampal regions (Jager et al., 2007; Nestor, Roberts, Garavan, & Hester, 2008). Further, two studies reported that MJ users exhibit reduced learning from errors, which is related to hypoactivity in the anterior cingulate, a region typically associated with cognitive control, a core component of executive function, and error awareness (Carey, Nestor, Jones, Garavan, & Hester, 2015; Hester, Nestor, & Garavan, 2009). Monetary incentive delay (MID) tasks, which examine reward processing, have shown that MJ use may also be related to brain circuitry involved in motivation and reward. Despite similar task performance on these measures, MJ users

exhibit hyperactivation within the striatum, a critical component of the reward system, during anticipatory stages of reward (Jager, Block, Luijten, & Ramsey, 2013; Nestor, Hester, & Garavan, 2010). However, this was predominantly due to increased levels during anticipation of neutral trials instead of reward trials (Jager, et al., 2013), suggesting an inability to disengage motivation despite a lack of reward. Van Hell et al. (2010) also utilized an MID task and reported that MJ users exhibited decreased activation during anticipated reward in the caudate and nucleus accumbens, and increased activation in the caudate and putamen during reward outcome compared to control subjects. Taken together, these findings indicate altered response patterns in MJ users to rewarding stimuli, which may be reflective of overly sensitive motivational brain circuitry.

Brain Structure

Brain imaging techniques have also afforded researchers the opportunity to examine the impact of MJ use on brain structure, including measures of both grey and white matter. Gray matter consists of neuronal cell bodies and is responsible for information processing and decision-making. White matter is comprised of nerve axons and controls the signals that neurons share and is critical for coordinating efficient communication between brain regions. Reviews documenting the structural impact of MJ use often report bidirectional findings, which are typically related to the brain region under examination (Batalla et al., 2013). Interestingly, however, alterations are most often observed in areas with high densities of CB1 receptors (Lorenzetti, et al., 2016) and may also be influenced by age of onset and increased MJ use (Filbey, McQueeney, DeWitt, & Mishra, 2015). In a recent review, Lorenzetti et al. (2016) found that while larger cerebellar and striatal volumes have been observed in MJ users, regular MJ users often exhibit reductions in grey matter volume in several other regions, particularly in the hippocampus. Importantly, studies have found that structural alterations in a number of brain regions appear to be related to increased executive dysfunction (Churchwell, Lopez-Larson, & Yurgelun-Todd, 2010; Medina et al., 2009; Medina, Nagel, & Tapert, 2010; Price et al., 2015) and poorer verbal memory (Ashtari et al., 2011).

White matter has also been assessed among MJ-using populations. In general, reduced white matter fiber tract integrity, measured using diffusion tensor imaging (DTI) techniques, has been observed in several prefrontal, limbic, parietal and cerebellar tracts in adolescent and emerging adult MJ users (e.g., Clark, Chung, Thatcher, Pajtek, & Long, 2012; Epstein and Kumra, 2015; Gruber, Dahlgren, Sagar, Gonenc, & Lukas, 2014; Gruber, Silveri, Dahlgren, & Yurgelun-Todd, 2011), and a relationship between earlier age of onset of MJ use and lower white matter integrity has been reported (Clark, et al., 2012; Epstein and Kumra, 2015; Gruber, et al., 2014; Gruber, et al., 2011). Moreover, these alterations have also been correlated with impulsivity (Gruber, et al., 2014; Gruber, et al., 2011) and appear to be a risk factor for poorer executive function and cannabis use disorders (Clark, et al., 2012).

Despite the noted impact on measures of brain structure and function, it is imperative to consider additional factors, which may influence findings and account for some of the heterogeneity observed across studies. As discussed below, it is likely that age of onset of

use, variables related to MJ exposure, chronological age, length of abstinence and chronological age each moderate the effects of MJ on the brain.

Variables Moderating the Impact of MJ Use on the Brain

Age of onset of MJ use

As noted, overall, investigations have revealed functional and structural alterations associated with MJ use, but a number of studies have also reported that decrements observed in adults tend to be more significant or persist for longer periods in those who began using MJ during adolescence (Jacobus, et al., 2009; Schneider, 2008). This is perhaps not surprising given the vulnerability of the developing brain. Additionally, some investigations have noted that earlier age of MJ onset appears to be inextricably linked to higher frequency and magnitude (grams used) of MJ use, suggesting that increased MJ use may be a trait characteristic specific to early onset users (Sagar, et al., 2015). As such, individuals with earlier MJ onset may have an “additive vulnerability,” marked by a brain that is susceptible to the impact of MJ coupled with an increased likelihood to engage in higher levels of MJ use, relative to those with later MJ onset. Age of MJ onset is therefore an important variable to include in research investigations as individuals who begin using MJ during adolescence are characterized by relatively “immature” brains and a tendency to use MJ more regularly, potentially posing a greater risk for cognitive decrements. Further, as differences between MJ users and non-users are often attributable to those with early versus late MJ onset (Ehrenreich et al., 1999; Fontes, et al., 2011; Gruber, Sagar, Dahlgren, Racine, & Lukas, 2012; Pope et al., 2003), collecting data regarding onset of MJ use is likely to help reduce heterogeneity of study findings in future investigations.

Exposure to MJ: Frequency, Magnitude, Potency & Novel Modes of Use

Increased frequency and magnitude of MJ use have been shown to predict poorer cognitive performance. For example, earlier age of onset and increased frequency (smokes/week) and magnitude (grams/week) of MJ use have been shown to be predictive of poorer performance on the Wisconsin Card Sorting Test (Dahlgren, et al., 2016) and Stroop Color Word Test, two robust measures of executive function (Dahlgren, et al., 2016; Sagar, et al., 2015). As the majority of studies regarding MJ use have examined the impact of heavy, chronic MJ use, conclusions regarding the effects of MJ use on the brain are generally reflective of chronic, recreational use and may not necessarily be generalizable to light or more casual MJ users. However, it is important to recognize that there is no consensus regarding the definition or criteria required for “chronic,” “regular,” or “heavy” use versus “casual” or “light use.” Discrepancies among what constitutes heavy relative to light MJ use has likely contributed to mixed findings across studies. Further, although most studies base assessments of MJ use on current number of days of use or number of episodes of use per week, some investigators utilize estimates based on longer periods of time, such as lifetime smoking episodes. Each of these definitions account for frequency of use, but none specifically account for magnitude or amount of cannabis consumed, which can be difficult to assess. Despite a number of reliable measures of problems associated with MJ use, few of these inventories are available for assessing frequency, magnitude, product type, route of administration, potency, age of onset of use, and other variables likely to impact study

results. Unlike alcohol and some other drugs, there is no standardized measure of MJ, which stems from a variety of difficulties in calculating exposure to MJ. For example, some derive the magnitude of MJ consumed by calculating the total number of joints smoked or “puffs” taken, while others calculate an estimate of actual grams of MJ used, which is becoming increasingly difficult with the advent of novel products and modes of use. However, even if individuals can quantify the number of grams of MJ used, it does not account for other factors that influence overall exposure.

Individuals often use MJ products of various strengths, or potencies. Over the last several decades, the potency of recreational MJ, measured as THC concentration, has increased exponentially. From 1995 to 2012, average THC levels in MJ products rose from approximately 4% to 12%, representing an increase of nearly 200% (ElSohly, et al., 2016). Although one study showed that individuals who smoke high potency MJ flower titrate their use to receive less THC (Freeman et al., 2014), some suggest that despite attempts to titrate high potency products, users are still exposed to higher amounts of THC than those using lower potency products (van der Pol et al., 2014), while still other studies have shown that individuals do not adjust their use when using higher potency products (Chait, 1989). Increased exposure to THC has also been associated with increased symptoms of cannabis use disorders (Freeman and Winstock, 2015; van der Pol, et al., 2014), increased risk for of psychosis (Di Forti et al., 2015; Large and Nielssen, 2017) and, as observed in acute administration studies, impaired cognition (D’Souza et al., 2004; Kowal et al., 2015; Ramaekers et al., 2006). In addition, one study assessing the relationship between brain structure and potency of MJ flower products, classified as either “high” or “low” potency by self-report, noted alterations in corpus callosum white matter microstructure in high-potency MJ users compared to low-potency users and controls (Rigucci et al., 2016). Studies assessing the impact of high vs. lower potency flower, which include laboratory analyses of products, used are needed.

Relative to traditional smoking methods, alternate modes of use like “vaping” are common and typically result in “more effect” from the same amount of cannabis (Malouff, Rooke, & Copeland, 2014). In addition, MJ concentrates have become increasingly popular. These products are made by extracting THC from MJ flower to yield products with extremely high levels of THC that can reach or exceed 80% (Stogner and Miller, 2015). Concentrated products all have significantly higher potency relative to conventional flower products (Mehmedic et al., 2010), and are often consumed through a process called “dabbing,” in which a “dab” (i.e., shatter, wax, butter, etc.) is placed on a rig with an extremely hot surface, and the user inhales the vapor, delivering a single, extremely high dose of THC in a single bolus. Although no studies thus far have directly examined the impact of concentrates on the brain, survey studies have associated the use of concentrates with negative physiological consequences (Cavazos-Rehg et al., 2016), stronger intoxicating effects (Loflin and Earleywine, 2014), and higher levels of physical dependence (Meier, 2017), and self-reported depression and anxiety (Chan et al., 2017). Overall, findings suggest that use of high potency MJ products, including concentrates, may impart negative consequences on the brain. This raises concern that adverse consequences associated with MJ use may be more significant now than in the past, particularly among young users. Interestingly, as previously noted, recent work assessing the relative impact of THC and CBD has suggested that the

presence of CBD may help to minimize or protect the brain from harm typically associated with THC (Yucel, et al., 2016), raising questions about mandatory minimums in products available to consumers.

Taken together, consistent, valid and reliable data regarding frequency, magnitude, potency, and modes of MJ use will play a key role in reaching a more complete understanding of the impact of MJ and its constituents on the brain. Increased frequency and magnitude of use, the use of more potent MJ products, and routes of administration that deliver high doses of THC quickly are all likely to impart negative neurobiologic consequences, particularly in areas of the brain previously shown to be affected by MJ use, which may, in turn, negatively impact cognitive processes sensitive to MJ exposure, including memory and executive function.

Length of abstinence

Throughout the literature, studies have employed a range of abstinence periods, generally ranging from 12 hours to one month, in order to examine the residual effects of MJ use, which may also influence study findings, as studies have shown changes in cognition over the course of abstinence periods. For example, Pope et al. (Pope, Gruber, & Yurgelun-Todd, 2001) examined chronic MJ users and noted no significant differences in cognitive performance compared to control subjects following a 28-day abstinence period, and more recently Fried and colleagues (2005) found that adolescent MJ users who abstained for at least three months demonstrated similar cognitive performance relative to healthy controls, providing evidence that abstinence may result in reversal of cognitive decrements. Although emerging evidence suggests recovery of cognitive function after relatively brief abstinence periods, others have shown that decrements are sustained over time (for review: (Ganzer, et al., 2016). Additional research is needed in this area, particularly studies examining the impact of *extended* abstinence periods (i.e., at least 6 months of abstinence) on cognition, brain structure and function. By examining MJ users after extended periods of abstinence, researchers can more closely examine the time course associated with potential normalization across specific cognitive domains, which may help address heterogeneous findings noted among MJ-abstinence studies. For example, it is possible that some cognitive decrements remit rather quickly and then plateau after only moderate improvement, while others may take longer to improve, fail to improve, or demonstrate yet another pattern following cessation of MJ use.

Chronologic Age: the impact of MJ use in older adults

Historically, increasing rates of MJ use have been noted among adolescents and young adults, which raised public health concerns given their neurodevelopmental vulnerability, driving research efforts to focus on youth and young adult populations. Recently, however, with expanded legalization across the US for both medical and recreational use, rates of use are now climbing fastest among older adults. According to data from the annual National Survey of Drug Use and Health (NSDUH), from 2002–2014, the proportion of adults aged 55 to 64 who reported MJ use in the past year increased by 455% from 1.1% to 6.1%; among those 65 and older, this proportion also increased dramatically, rising from 0.3% to 1.3% (Azofeifa et al., 2016). In comparison, rates among 18- to 25-year-olds rose only 7%

in the same period, while 12–17-year-olds actually *decreased* 17%. Despite the prevalence of MMJ use among older adults, consequences of use are relatively unknown in this population, although preclinical evidence suggests that THC may impact older individuals differently. A recent study reported a *reversal* of age-related cognitive decline in mature and old mice treated with low doses of THC, while the same exposure resulted in cognitive decrements among young mice (Bilkei-Gorzo et al., 2017). It is possible that the improvements noted in mature and older mice reflect an upregulation of the aging eCB system via increased signaling secondary to low-dose THC exposure. It is of note, however, that older adults may also have specific vulnerabilities with regard to MJ use. As overall metabolism slows with age (O'Malley, Crooks, Duke, & Stevenson, 1971), MJ may take longer to “clear the body,” increasing the likelihood of experiencing higher levels of intoxication or an adverse event. Further, cannabinoids, including CBD, can inhibit the liver's cytochrome P450 enzyme system, increasing both plasma levels and toxicity of other drugs and potentially causing drug-drug interactions (Zendulka et al., 2016). This is important as approximately one-third of all prescription drugs in the US are used by older adults (NIDA Community Drug Alert Bulletin: Prescription Drugs, 2005). Additional studies aimed at identifying the specific impact of MJ use in older adults are clearly warranted, especially given the shifting landscape of legal recreational and medical use in a growing number of states.

Can the Effects of Recreational MJ Use be Generalized to MMJ Use?

THC is the most commonly studied cannabinoid, due in part to its role as the primary psychoactive constituent of MJ, which drives the recreational consumer. In contrast, MMJ users are often inclined to seek products with varied cannabinoid constituent profiles, including those with high levels of CBD and other cannabinoids. While CBD has demonstrated the potential to mitigate some of the negative effects related to THC (Yucel, et al., 2016) and has tremendous therapeutic potential for a variety of conditions and indications (Whiting, et al., 2015), studies investigating the properties of additional cannabinoids, including cannabigerol (CBG), cannabichromene (CBC), and cannabinol (CBN), also cite positive effects, such as anti-inflammatory and neurogenic effects (Borrelli et al., 2013; Izzo, et al., 2009; Shinjyo and Di Marzo, 2013; Valdeolivas et al., 2015). In addition to the unique effects of each individual cannabinoid, many posit the existence of an “entourage effect,” which describes the synergistic effects of multiple cannabinoids and terpenoids (Russo, 2011). Terpenoids, the essential oils responsible for the flavor and fragrance components of cannabis, share a common precursor with phytocannabinoids and also likely exert their own biobehavioral health effects. The entourage effect may help explain why products from whole-plant extractions appear to be more efficacious than isolated cannabinoid compounds (Gallily, Yekhtin, & Hanuš, 2015).

Although additional research is needed to fully understand the effects of individual cannabinoids as well as interactions among cannabinoids and terpenoids, potential differences between recreational and medical users' product choices raise the question as to whether the effects of recreational MJ use can be generalized to MMJ use. Despite the literature on recreational MJ use, few studies thus far have specifically examined the impact of MMJ on the brain, which may differ from recreational use given a number of factors.

Recent work suggests that following three months of MMJ treatment, patients exhibit improvements in mood, quality of life, and sleep disturbance as well as *improved* cognitive performance on measures of executive function relative to baseline (Gruber et al., 2018; Gruber et al., 2016). Additionally, in the first study to use neuroimaging techniques to examine functional correlates of MMJ use, three months of MMJ treatment was related to apparent normalization of brain activation in two regions of interest (ROIs), during the completion of the Multi-Source Interference Test (MSIT), a robust measure of cognitive control, which reflects the ability to inhibit an automatic response tendency in favor of a less automatic response (Gruber, et al., 2018). Specifically, prior to initiation of MMJ treatment, patients did not show activation in the cingulate cortex, a region typically activated during completion of the MSIT in healthy controls (Bush and Shin, 2006; Gruber, Dahlgren, Sagar, Gonenc, & Killgore, 2012). Interestingly, after three months of treatment, MMJ patients exhibited significant cingulate activation as well as increased activation in a frontal ROI, which consisted of superior frontal, middle frontal, and inferior frontal gyri. As these changes in brain activation occurred in the context of improved task performance and resemble that of healthy control participants, results may reflect a normalization of brain activity. These improvements, which are in stark contrast to previous findings in recreational MJ users, particularly those with adolescent onset, may be related to protective factors such as the presence of CBD and other therapeutic cannabinoids in MMJ users' products or attributable to the age of MMJ patients, who are typically older than recreational users who most often begin using MJ during adolescence or emerging adulthood. Further, both studies of MMJ patients (Gruber, et al., 2018; Gruber, et al., 2016) reported symptom alleviation and a notable decrease in conventional medication use following 3 months of MMJ treatment, which also have contributed to study findings. Additional research is needed to fully explore mechanisms of action in recreational and medical MJ users in order to identify those specific factors which exacerbate and those which protect against the potential adverse effects of MJ primarily observed in young, recreational users.

Marijuana and Public Policy

The rapid pace of legalization efforts has caused policy to outpace science, and while additional research is needed, it is imperative to use scientific evidence to guide policy decisions. In a recent article, Fischer and colleagues (2017) outlined recommendations for "lower-risk" cannabis use. While several recommendations are tied to general health outcomes, relevant guidelines aimed to minimize the cognitive consequences associated with MJ use include the following: avoiding early age of onset of use, choosing low-potency THC products or those with a balanced THC:CBD ratio, refraining from high frequency of use, and avoiding the combination of any of these high risk factors. It is critical that these guidelines and the science that shaped these recommendations are considered in policy decisions.

For example, as previously noted, studies of recreational MJ use report decrements in cognitive performance and alterations in brain structure and function (Batalla, et al., 2013; Battistella et al., 2014; Broyd, et al., 2016; Crane, et al., 2013; Crean, Crane, & Mason, 2011; Filbey et al., 2014; Ganzer, et al., 2016; Gruber and Sagar, 2017; Lisdahl, et al., 2014; Lorenzetti, et al., 2016; Nader and Sanchez, 2017; Weinstein, Livny, & Weizman, 2016), and

many agree that individuals who begin to use MJ in adolescence or those with earlier onset of use are more likely to demonstrate neurobiologic alterations than individuals who initiate use later in life (Gruber and Sagar, 2017; Lisdahl, et al., 2013; Lisdahl, et al., 2014). These findings are tied to work demonstrating that the adolescent brain is not fully mature during adolescence and thus more vulnerable to the effects of drugs and alcohol than adults. As the prefrontal cortex is among the last of the brain regions to become fully mature (Casey, Galvan, & Hare, 2005), yet responsible for higher order executive functions, policymakers should carefully consider age-related guidelines to help prevent or reduce adolescent exposure. In addition, advertising of MJ products should not target youth, who are highly brand-conscious consumers, and safe guidelines for packaging of MJ products should be established to prevent accidental ingestion of edibles by children. In the midst of sweeping legalization efforts, many have questioned whether legalization of recreational and/or medical MJ itself increases access, and subsequently, rates of use among adolescents. While long-term investigations are still needed, data from the most recent Monitoring the Future (MTF) study, which has surveyed 8th, 10th, and 12th graders across the US since 1991, indicates that past-year MJ use has either remained unchanged or *decreased* across each grade in recent years, despite a decline in the perceived harm associated with regular MJ use (Miech, et al., 2017). Further, rates of daily MJ use also appear to either be holding steady or decreasing. However, additional research is needed both within the US and across the globe to clarify adolescent MJ use patterns in given increasing legalization of both medical and recreational/adult use MJ.

Policymakers are encouraged to engage in dialogue regarding safe limits of MJ use. In addition to frequency and magnitude of MJ used, safe limits of MJ use should consider potency of MJ products used and novel modes of administration, specifically those designed to deliver large doses of THC at once (i.e. ‘dabbing’). In the US, some states have considered increased tax rates for higher potency products or limiting the total amount of THC within products available, but to date no state has implemented these policies. Given that a number of cannabinoid constituents have potentially beneficial and neuroprotective effects, it is also important to determine whether implementing minimums for certain constituents, such as CBD, could help to mitigate some of the adverse effects related to THC. In light of research showing rising THC and declining CBD levels in recreational products, reversing this trend could prove to be a helpful step in public policy.

Barriers to Cannabis Research

In order to fully understand the potential benefit and possible risks associated with cannabis use, researchers must be able to *study actual cannabis products currently available to consumers* for both recreational and medical use. However, despite a growing need for information to help inform public policy and safe use guidelines for consumers and patients alike, a number of barriers currently hinder research efforts. First, in the majority of countries the status of MJ poses significant challenges. In the US, the landscape is particularly complicated; while MJ may be legal in a particular state for medical and/or recreational purposes, it remains illegal at the Federal level making it difficult for scientists to gain access to appropriate products for investigation. Although researchers are permitted to conduct studies using non-plant derived or synthetic formulations, these products may

lack ecological validity, raising concern with regard to generalizability of study findings. However, current US regulations stipulate that all cannabis (other than non-plant derived/synthetic products) to be used in clinical trials must be obtained from an approved Federal source, historically, the National Institute on Drug Abuse (NIDA). Although the US Drug Enforcement Agency (DEA) announced in 2016 that it would accept applications for non-NIDA entities to become registered to manufacture MJ and related products to supply researchers in the US, at this time, NIDA remains the only approved source of plant derived cannabis material for US-based researchers. Over the last several years, NIDA's Drug Supply Program (DSP) has exponentially expanded the number of conventional MJ flower products (and one high CBD extract) available to researchers, which vary in constituent composition (low, medium, high THC, CBD, etc.) and potency. Similar to non-plant derived products, investigations using only products from NIDA's DSP may also suffer from a lack of ecological validity, as potency and constituent ratios may not be consistent with consumers' products. Further, the majority of products available through the DSP are in conventional flower form, and do not reflect the wide range and types of products that MJ consumers and patients often use. In addition, quality may not be optimal given that many strains are frozen after harvest, and long-term storage of material may compromise product quality.

Importantly, recent findings also highlight issues of quality assurance in commercially available products, raising questions about their use in research investigations. Specifically, both THC and CBD content have been shown to be mislabeled (both over- and under-labeled) across product types (Bonn-Miller et al., 2017; Vandrey et al., 2017). Reporting lower levels of THC than actually contained in a product may result in adverse or unwanted reactions or experiences, while reporting higher levels of cannabinoids than actually contained may result in inadequate symptom relief or failure to achieve desired effects. If inconsistencies are noted among commercially available products, they may be rendered unsuitable for use within a traditional clinical trial model, which requires the use of products with known and consistent constituent profiles. Mechanisms allowing cannabis growers or providers to have batches of their products tested, vetted, and ultimately approved for use by researchers may help facilitate assessment of the impact of MJ products actually used by consumers.

Research in the US is also complicated by the fact that *all cannabinoids* derived from the cannabis plant, regardless of their diversion potential, fall under Schedule I of the Controlled Substances Act, the most restrictive category. This categorization persists despite the fact that numerous constituents, particularly CBD, are non-intoxicating and have been deemed "safe" by a number of sources (Iffland and Grotenhermen, 2017; Volkow, 2015, July 20). Accordingly, many have questioned whether this remains an appropriate classification, especially given the recent published report from the National Academy of Sciences, Engineering and Medicine (NASEM), which found "conclusive or substantial evidence that cannabis or cannabinoids are effective" for the treatment of chronic pain, chemotherapy induced nausea and vomiting, and muscle spasticity symptoms of multiple sclerosis (The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research, 2017). In addition, there is also mounting evidence that CBD is beneficial for the treatment of intractable pediatric epilepsy and related disorders

(Devinsky et al., 2016; Press, Knupp, & Chapman, 2015), and some studies have shown that CBD holds promise as a potential treatment for anxiety (Blessing, et al., 2015) or even as an adjunctive therapy for psychotic symptoms in schizophrenia (Gruber, et al., 2016; McGuire et al., 2017; Piper et al., 2017; Reiman, Welty, & Solomon, 2017; Vigil, Stith, Adams, & Reeve, 2017). By virtue of its Schedule I classification at the Federal level, MJ is considered more dangerous than substances such as cocaine, methamphetamine, and opioids. In fact, the US is in the midst of an opioid epidemic; the rate of opioid overdose deaths, including those related to both prescription pain relievers and heroin, is five times higher than in 1999 (Hedegaard, Warner, & Miniño, 2017). Ironically, some studies have shown that MMJ patients often report *decreased* use of prescription opioid medications (Gruber, et al., 2016; Piper, et al., 2017; Reiman, et al., 2017; Vigil, et al., 2017), states with MMJ programs report fewer opioid prescriptions written (Bachhuber, Saloner, Cunningham, & Barry, 2014) and fewer opioid overdoses (Bradford and Bradford, 2016), and NIDA has identified the eCB system as a potential target for opioid withdrawal, suggesting that cannabis-based products may have the potential to help alleviate this epidemic. Unfortunately, as a result of MJ's classification as a Schedule I substance, few trials have been conducted regarding the effects of MMJ and the relationship between MJ and opioid use.

Finally, it is critical to recognize that not all MJ is "the same," which can introduce a number of variables into research studies, many of which are difficult to control for without targeted queries or laboratory analyses. There are countless strains of MJ flower, with varied potencies and diverse cannabinoid and terpenoid profiles. Each of these products likely exerts a unique effect given not only the specific impact of each cannabinoid and constituent ratios, but also the potential for entourage effects. Given the variability in MJ constituents across strains and products, laboratory testing of consumers' MJ products can provide important insights into the unique effects of specific cannabinoids. In addition to collecting this type of objective information about cannabinoid content, researchers are also encouraged to specifically query about age of onset, frequency, and magnitude of use in quantifiable ways in order to achieve estimates of overall exposure to MJ, especially when laboratory analyses are not conducted or are unavailable. Further, whenever possible, both in-house drug assays, which assess for the presence or absence of multiple substances, and (when applicable) laboratory analyses of urine or blood samples for absolute quantification are essential for validation and interpretation of study results.

Overall, a number of barriers limit MJ-related research in countries where MJ remains illegal at the national level. However, research is critical for safety and efficacy assessments of medical MJ products, and to examine the impact of these products on the brain. For example, in the US, there is currently no mechanism under which researchers can directly assess the impact of widely available, hemp-derived products. Although dozens of products are available in stores and online for shipping to all 50 states, it is currently against Federal regulations to use hemp-derived products in a clinical trial. Accordingly, despite countless thousands of consumers providing anecdotal reports of improvement following the use of these products, empirically sound, clinical trial models are needed to support or refute these claims and to examine safety and efficacy. As a result of regulatory hurdles, many researchers are left to conduct observational trials when studying *plant-derived* MJ treatment or products. While these studies attempt to control for confounding variables and may utilize

a pre vs. post or longitudinal design, without the ability to randomize subjects into treatment or control groups, and no ability to control product type, dose, or frequency, conclusions may be limited. Cross sectional studies of recreational MJ users suggest that MJ use is related to neurobiologic alterations such as decrements in cognitive performance and altered brain structure and function. As previously noted, this may not be the case in MMJ patients; (Gruber, et al., 2018; Gruber, et al., 2016); clinical trial models would help clarify this issue and potentially identify specific associations between individual cannabinoids and these neurobiologic variables.

Countries that have not been faced with the same legal restrictions have been able to conduct groundbreaking research. Israel serves as a prime example; although MMJ was only legalized in Israel nearly 20 years ago, Israeli scientists have been at the forefront since the 1960s when THC was discovered, and later when the human eCB system was elucidated (Mechoulam, 2015). Since then, researchers in Israel have continued to conduct investigations that help clarify the potential benefits of MJ for various medical conditions (Mechoulam, 2016). Uruguay is also positioned to partner in MJ-related research projects given their recent national legalization. As MJ legalization efforts march forward, scientists in countries with fewer restrictions and research barriers will likely continue to have the greatest opportunities to help bridge the growing gap between policy and science.

Conclusions

Decades of research have focused on the impact of recreational MJ use, documenting decrements across various cognitive domains (e.g., memory, executive function, and likely processing speed) as well as structural and functional brain alterations which often underlie poorer cognitive performance or suggest inefficient processing in chronic, heavy users. These changes are most evident among adolescent users or those with early onset of MJ use, as adolescence represents a critical period of neurodevelopment, making youth more vulnerable to exogenous influences, including MJ. Accordingly, frequency and magnitude of use, product choice/potency, mode of use, and age of the consumer are all likely to influence the effects of MJ on the brain. It is important, however, to recognize that cannabis is a diverse and complex plant comprised of numerous constituents, which exhibit unique effects when studied alone as well as in the presence of other cannabinoids. Despite the range of effects conferred by individual constituents, many of which are non-intoxicating and have no diversion potential, cannabis is currently treated as a single entity and classified as a Schedule I substance, the most restrictive drug class, significantly hindering research efforts. While recreational use among adolescents and early onset users is relatively well studied, a number of areas remain understudied. For example, future investigations are needed to clarify the impact of MMJ on the brain, short- and long-term consequences of high potency products and novel modes of use, effects of MJ use in older adults, and the efficacy and safety of existing products as well as those in development, ideally using clinical trial models. As the nation has warmed toward the idea of MJ for both medical and adult recreational use, the need for empirically sound data is critical to help patients and consumers make informed decisions about their use.

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