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Cannabis effects on brain structure, function, and cognition: considerations for medical uses of cannabis and its derivatives

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Abstract

Background—Cannabis is the most widely used illicit substance worldwide, and legalization for recreational and medical purposes has substantially increased its availability and use in the United States.

Objectives—Decades of research have suggested that recreational cannabis use confers risk for cognitive impairment across various domains, and structural and functional differences in the brain have been linked to early and heavy cannabis use.

Methods—With substantial evidence for the role of the endocannabinoid system in neural development and understanding that brain development continues into early adulthood, the rising use of cannabis in adolescents and young adults raises major concerns. Yet some formulations of cannabinoid compounds are FDA-approved for medical uses, including applications in children.

Results—Potential effects on the trajectory of brain morphology and cognition, therefore, should be considered. The goal of this review is to update and consolidate relevant findings in order to inform attitudes and public policy regarding the recreational and medical use of cannabis and cannabinoid compounds.

Conclusions—The findings point to considerations for age limits and guidelines for use.

Keywords

Cannabis; brain; morphology; endocannabinoid; tetrahydrocannabinol; cannabidiol; medical marijuana; cognition

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The authors have no interests to declare.

Introduction

Cannabis *(Cannabis sativa)* has been used for centuries as a source of fibers, food, oil, and medicine, as well as for recreational and religious purposes (1). It contains over 500 identified natural compounds, including cannabinoids, terpenoids, flavonoids, and alkaloids (2,3). Among these, Δ^9-tetrahydrocannabinol (THC), the primary psychoactive ingredient, has promoted widespread recreational use and misuse of the plant. Cannabis is the most widely used illicit substance worldwide, with an estimated 183 million past-year users in 2017 (4). In the United States, 18% of persons 12 or more years of age reported previous month use, and 1.5% in this age category met diagnostic criteria for Cannabis Use Disorder (4). The Drug Enforcement Agency has placed cannabis in Schedule I of the Controlled Substances Act, but 10 states have legalized its recreational use, and 32 have legalized its use for medicinal purposes.

Because of the increased and widespread availability and use of cannabis, and FDA-approved medical uses of cannabinoid compounds, information regarding potential untoward effects and safety limits is needed to guide public policy. Of primary concern are potential effects on the brain and cognition, which are reviewed here.

Cannabis and the endocannabinoid system

The endocannabinoid system is phylogenetically old, having been identified in the most primitive animals with a neuronal network. In animals, N-arachidonoylethanolamine (anandamide) and 2-arachidonoyl glycerol (2-AG) are the major endocannabinoids. Many of their effects and those of phytocannabinoids are mediated by CB1 and CB2 receptors, which primarily couple to G proteins of the G_i and G_0 classes, although some cannabinoids engage other receptors (i.e., transient receptor potential channels and peroxisome proliferator-activated receptors) (5,6). CB1 receptors, which mediate many of the psychoactive effects of cannabinoids, are found in high densities in several brain regions and the eye, and in lower densities throughout the body (6,7). Among the most abundant G protein-coupled receptors in the brain (5), they are localized primarily to neurons but also are expressed in glia (8). CB2 receptors are found in immune cells and in some neurons. The endocannabinoid system comprises these receptors, the endocannabinoids anandamide and 2-AG, and the enzymes that regulate their production and degradation (9,10).

Within the brain, CB1 receptors are expressed in cortical areas involved in higher cognitive functions, midbrain regions associated with motor control, and hindbrain regions that participate in control of motor and sensory functions of the autonomic nervous system (11). The endocannabinoid system plays a role in homeostasis and neuroplasticity, including neurogenesis and refinement of neuronal connections (12–14). Increased endocannabinoid signaling is associated with reduced stress response, improved emotion regulation, and increased reward signaling (12,15). Endocannabinoids modulate the function of diverse neurotransmitter systems, some of which may have opposing roles. To the extent that exogenously administered cannabinoids affect the same targets, the effects can resemble or diverge from those of endogenous cannabinoids depending on the respective actions at relevant receptors. Notably, the generally high potency of synthetic cannabinoids relative to

the natural psychoactive Δ^9-tetrahydrocannabinol (THC) in cannabis has led to substantial problems with toxicity (16).

THC acts as a partial agonist with high affinities for both CB1 and CB2 receptors (K_i = 10 nM and 24 nM, respectively). Autoradiographic and positron emission tomographic studies of the rhesus monkey and human brain have shown high densities of CB1 receptors in the cerebral cortex (cingulate gyrus, middle frontal gyrus, entorhinal cortex, and Wernicke's area), hippocampus, caudate/putamen, globus pallidus, substantia nigra, and cerebellum (17,18). This receptor distribution is consistent with the psychoactive actions of THC and thereby with potential effects of cannabis on memory, stress-responsivity, reward, and motivated behavior, as well as self-monitoring.

The localizations of cannabinoid receptors also are consistent with important roles in reward, reinforcement, and addiction. CB2 receptors are expressed in dopamine neurons of the midbrain ventral tegmental area (19), where effects on THC receptors may modulate addiction-related behaviors, such as drug reinforcement (19). CB1 and *mu* receptors are co-localized in striatal output projection neurons of the nucleus accumbens and dorsal striatum, which modulate reward and habit formation, respectively (20).

CB1 and CB2 receptors are expressed from early embryonic stages, and there is evidence that endocannabinoid tone is dynamically regulated during neurogenesis, and that CB1 receptors have a regulatory role in the development of the embryologic neural system (21,22). Although findings regarding effects on infant behavior and cognition are inconsistent, evidence suggests that prenatal cannabis exposure can influence neuronal maturation and cognitive function later in life (23). Because brain development continues to proceed through adolescence and early adulthood (24,25), the rising use of cannabis in these age periods raises concerns.

Unlike THC, which is psychoactive and is self-administered by rats (e.g. (26),), CBD is considered non-psychotropic and inhibits drug-seeking and self-administration in animal models (26,27). CBD does not bind to the orthosteric binding sites of CB1 and CB2 receptors with high affinity (27–29), but acts as an allosteric inhibitor of both cannabinoid receptors subtypes (27,30,31). Recent evidence indicates that CBD is a negative allosteric modulator at CB1 receptors and a partial agonist at CB2 receptors (32). CBD also is an allosteric modulator of *mu* and *delta* opioid receptors (33). Through these mechanisms, CBD may modulate opioid actions and addiction vulnerability.

Effects on brain structure

Most information on the impact of cannabis use in humans that has come from studies of individuals with chronic, heavy recreational use, and relevant reviews from 1976 to 2002 have presented some inconsistencies regarding effects on brain structure (34–37). Structural neuroimaging studies provide evidence of morphological abnormalities in chronic adolescent as well as adult users (38,39); these effects may be related to the amount of cannabis exposure. One might predict that the brain regions with the highest densities of CB1 receptors would show changes due to heavy cannabis use. CB1 receptors are expressed at high levels in the temporal lobe (olfactory system, the hippocampal formation, and

amygdala), the cerebellum and neocortex, and are expressed widely at lower levels in other brain regions (6,40,41).

Within the temporal lobe, which has a high density of CB1 receptors, studies have focused on the hippocampus. Despite some inconsistencies across study designs and in findings (42), structural neuroimaging has indicated abnormalities in hippocampal volume (43–47) and gray matter density (48,49) of cannabis users relative to controls. Hippocampal atrophy was noted even after more than 6 months of supervised abstinence in 14 young adults with a history of heavy cannabis use (5.8 joints/day) (43). While one study reported no significant differences in hippocampal volume (50) between 22 long term, heavy cannabis users and 26 non-users, others reported finding smaller hippocampal and amygdala volumes associated with long-term cannabis use (46,47). Additionally, a longitudinal study of 20 heavy cannabis users, who reported smoking cannabis more than 5 days a week, did not find hippocampal volume alterations in cannabis users compared to controls at either baseline or at an average of 39-months post-baseline (51).

Other work showed that abnormalities in hippocampal volume and shape may be seen in individuals who have cannabis dependence, and not necessarily in those who engage in regular cannabis use without exhibiting dependence (52). Nonetheless, several review articles in the past decade (53–55) have concluded that *chronic* cannabis use has a significant effect on hippocampal structure in adolescents and suggested that such effects reflect interactions with cannabinoid CB1 receptors, which are densely expressed in the hippocampus.

There are indications that frequent cannabis use may be particularly harmful to the adolescent brain (56). It is plausible that those who begin cannabis use early in adolescence would be more likely to become heavily dependent. Early, heavy use may then interfere with educational and vocational training, leading to long-term consequences in adulthood. From a more biological perspective, use of cannabis during critical developmental periods may cause persistent, long-term alterations in brain structure and brain function. Some studies suggest that the effects of cannabis use during adolescence could be more serious than during adulthood (57) because it may alter the trajectory of brain development (24).

Recent findings indicate that changes to hippocampal structure due to heavy cannabis use, starting in adolescence, persist well into adulthood even following abstinence for several decades (45). These changes are regionally specific to hippocampal subregions with high densities of CB1 receptors, and are not seen in parietal cortex, where the density of CB1 receptors is relatively low. Although obtained in a retrospective assessment, these results argue for more long-term prospective studies to examine the effects of adolescent use in late life, to help clarify how changes resulting from heavy cannabis use interact with brain aging.

Assessments of brain regions other than the hippocampus have revealed disparate results. Several reports found no group differences in amygdala volume (43,58–62), but according to one report, the amygdala was 7.1% smaller in users than in controls (47). A large study of 22–35-year-old participants (483 in all, 282 reporting having ever used cannabis) found smaller left amygdala and right ventral striatum volumes; but the differences were within the

range of normal variation, and the apparent effect on amygdala was largely attributed to shared genetic factors (63).

A study of young adults found that 20 recreational cannabis users had greater gray matter density than in 20 controls in the left nucleus accumbens extending to subcallosal cortex, hypothalamus, sublenticular-extended amygdala, and left amygdala, with shape differences in the left nucleus accumbens and right amygdala (59). Yet a recent, large study of two population-based samples 622 young Australian adults [66% female] and 474 middle-aged US males found no differences in cannabis users compared with controls in subcortical volumes (putamen, caudate, pallidum, hippocampus, amygdala, nucleus accumbens, and thalamus) (64).

Other subcortical assessments found that cannabis users had similar (60,62) or larger cerebellar volumes (44,58) than nonusers. Finally, there is some evidence for damage to white matter in specific brain regions of cannabis users as compared with controls, possibly reflecting demyelination or axonal damage resulting in altered brain connectivity and functional impairment (65–68).

A multi-site MRI study in long-term cannabis users found no association between cannabis use and cortical morphology (52). Three studies found smaller orbitofrontal cortical volume in cannabis users compared to controls (44,69,70), whereas three other studies did not (58,60,71). In a recent study, gray- and white-matter volumes, cortical thickness, and gray matter density were measured in a relatively large sample of adolescent to emergent adult cannabis users: n = 147 (109 occasional users [<1–2 times/week] and 38 frequent [>3 times/week]) as compared with 634 non-users (72). No significant group differences in global or regional brain volumes were noted; the authors suggested that discrepancies with prior positive findings reflected differences in dose metrics in young cannabis users.

Although the majority of the relevant structural neuroimaging studies investigated the results of heavy, chronic cannabis use, a recent investigation showed that 46 adolescents (14 years old) who used cannabis only once or twice showed greater gray matter volume in bilateral medial temporal lobes, posterior cingulate, lingual gyri, and cerebellum (73). The authors offered that, although cannabis use has typically been associated with below control brain volumes, most previous neuroimaging research on cannabis effects involved participants who had heavy substance use histories.

Increasing usage rates by people in every age range in the United States (74,75) highlight the need to address unanswered questions about the effects of cannabis on the brain (see Table 1). Legalization has enhanced public awareness of questions about the effects of cannabis, and may also facilitate the recruitment of participants for observational studies to answer these questions. Rapidly advancing data collection supported by funding for large-scale longitudinal studies, such as the Adolescent Brain Cognitive Development Longitudinal Study, will be addressing many of these questions (Collaborative Research on Addiction at NIH).

Investigators conducting these longitudinal studies or using translational animal models of developmental cannabinoid drug exposure are encouraged to enable assessment of causality

in associations between cannabis use and alterations in brain structure and behavior. Animal models of cannabis inhalation (vs. injection) in preclinical studies may facilitate translation of results to the human population.

Cannabis effects on brain function

There is accumulating evidence that regular cannabis use can alter brain function, especially in networks that support working memory, attention, and cognitive control processing (76). Several prior reviews have addressed the functional impact of chronic cannabis use in both adults and adolescents (38,71,77,78). Functional MRI (fMRI) paired with cognitive testing typically has demonstrated abnormalities in brain activity, although the results have varied with study parameters (77), inter-subject variation (79), and amount of cannabis use (80). In comparisons of adult chronic cannabis users with healthy controls, neural activation was measured in paradigms including tests of attention (81), cognitive control (78,80), memory (82–84), decision-making (85–88), motor performance (89) and affective processing (90). Most of these studies have revealed changes in brain function, often without notable performance deficits, suggesting that performance may be maintained through recruitment of brain regions not typically engaged in a particular cognitive function. In contrast, schizophrenic patients with cannabis abuse had better emotional memory than schizophrenic patients who did not use cannabis, possibly by reducing negative symptoms (91).

In task-based fMRI, a response-inhibition task showed greater connectivity between a right frontal control network and substantia nigra-subthalamic nucleus network in cannabis-dependent users compared to nondependent users (69). Another study used fMRI data form 158 20-year-old men, whose cannabis use had been tracked during adolescence. Brain activity was measured while they performed a card-guessing game that assessed responses to anticipation and receipt of monetary reward (92). Functional connectivity of the nucleus accumbens to the medial prefrontal cortex was influenced by the trajectory of cannabis use during adolescence. Among the participants, those that were identified as having an escalating trajectory showed a pattern of negative functional connectivity between the nucleus accumbens and medial prefrontal cortex activity was linked to higher levels of depressive symptoms, anhedonia, and lower educational achievement. The authors suggested that cannabis use in adolescence may have consequences for mood symptoms and educational achievement in early adulthood via alterations in neural reward circuitry.

Several investigations have compared differences between cannabis users and nonusers in functional brain networks, both during task performance and in the resting state, when fMRI was used in the absence of a task. Adult cannabis users generally differed from controls in resting-state functional connectivity (for review see (93)). Cheng et al. (94) used a two-level multi-voxel pattern analysis of resting state fMRI data to classify cannabis users from control participants with an accuracy rate of 84–88% in predicting whether a single participant was a cannabis user. In another study, adult cannabis users showed stronger functional connectivity compared to controls within the default mode network, and this difference persisted after 1 month of abstinence (95). Another study found differences in resting state connectivity of the middle frontal gyrus, precentral gyrus, superior frontal gyrus, posterior cingulate cortex, cerebellum and some other regions of male heavy cannabis

users compared with controls (94). Also, psychophysiological interaction analysis indicated that functional connectivity (but not regional activation) in the reward network differentiated dependent from non-dependent cannabis users in a cannabis cue paradigm (76). Finally, functional connectivity of the ventral striatum and midbrain, key brain areas for reward circuitry, as well as the brainstem and lateral thalamus was stronger in cannabis users than in controls (38,71,96).

In adolescents, heavy cannabis use was most commonly linked with abnormal frontoparietal network activity, but these findings may reflect a compensatory mechanism, particularly in prefrontal cortex (97–103), to maintain behavioral performance. Studies of memory (84,104,105), attention (106), decision-making (107), and inhibitory control (108) in adolescents all demonstrate abnormal functional activation patterns. Similar to studies in adults, many task-based fMRI studies also found intact behavioral performance (88,89,106,109,110) in adolescent cannabis users compared to controls. Thus, the adolescent brain apparently achieves some level of reorganization, engaging regions not typically involved in performing a particular task (71,105). Whether such a compensation extends into adulthood after prolonged usage is questionable, and a mechanistic clarification of how long-term usage and prolonged functional brain alterations transform behavioral or cognitive output will require further investigation.

The application of fMRI is only beginning to address the neural mechanisms associated with the cognitive consequences observed in cannabis users, and more work is needed to elucidate the links between cannabis use, brain function and cognitive output. Factors to consider in future research include age of onset, mode of use, frequency and extent of cannabis use, recovery of function with abstinence, composition of the cannabis product. The implications of functional brain changes resulting from cannabis use are yet to be determined, but changes in brain activity may be an early indicator of long-term consequences before cognitive deficits are measurable (42).

Cannabis use and cognition

Research to date has suggested that acute and chronic use of cannabis leads to cognitive impairments (111,112). Various factors, including sex differences and genetic variations may influence these effects (113,114).

Acute effects

There is substantial evidence that acute administration of cannabis or THC adversely affects executive function. On tasks of planning, reasoning, interference control, and problem solving, impaired performance was observed in some (115–120), but not all studies (121–123) of occasional, moderate and heavy users. In test of inhibitory control, such as go/no-go or stop-signal tasks, THC administration increased reaction time in occasional and heavier cannabis users (116,118,122,124), but other findings in chronic users were mixed (125–129).

Of concern are the effects of cannabis use on decision-making, especially when it involves risk-taking. Self-report questionnaires and laboratory risk-taking tasks have demonstrated differences between cannabis users and non-users, possibly related to the severity of

cannabis use. The Iowa Gambling Task, delayed discounting tasks, and risk-taking decision-making tasks have been used. Acute administration of THC altered sensitivity to reward and punishment and increased risk-taking behavior in infrequent (130) and regular users (120,131,132), but not all relevant studies found impaired decision-making.

Chronic effects

Mounting evidence points to cognitive impairment after chronic, heavy cannabis use (133–135), enduring beyond the acute effects, although there is also a large body of evidence with negative findings in cannabis users (136–138). In prospective studies of adolescents, findings regarding general intelligence are contradictory (56,139,140), but negative effects have been observed across a wide range of cognitive domains, including, but not limited to, various aspects of memory, executive function/working memory, and processing speed. Consistency in experimental design remains a challenging aspect of studying the long-term effects of chronic cannabis use on cognition (141).

Memory has been the cognitive domain most consistently impaired, with verbal learning and memory tasks particularly sensitive to the acute (142–144) and chronic (134) effects of cannabis. Several individual aspects of memory appear to be affected (46,134,145,146), with the most robust effects on verbal learning, including decrements in measures of encoding, recall, and recognition (see (134) for review). Associations between poorer performance in regular cannabis users and frequency, quantity, duration, and age of onset of cannabis use have also been reported (97,98,114,147,148). In long-term users, lasting impairments in memory and attention worsened with increasing years of regular cannabis use (135,140,149,150).

Contrary to these findings, recent studies have shown that THC can promote neurogenesis, restore memory and prevent neurodegenerative processes and cognitive decline in animal models of Alzheimer's disease (151–153). CBD also improves cognition in preclinical models of cognitive impairment in schizophrenia (154). To reconcile these seemingly contradictory results, it has been suggested that THC modulates memory and cognition in an age- and dose-dependent manner (155).

A systematic review cited evidence of deficits in attention or concentration and in memory function, with a trend toward impairments in inhibition, impulsivity, and decision-making in cannabis users (146). More cannabis use was linked with poorer episodic memory and decision-making but not inhibitory control, and sex-specific dissociations were apparent – amount of cannabis use more consistently associated with poorer episodic memory in females than males, but with poorer decision-making performance by males only (114). Notably, reviews of numerous studies of young cannabis users concluded that regular use during the adolescent and emerging adult periods may produce lasting negative effects on cognitive functioning and IQ (140,156,157). However, several recent studies have found no evidence that adolescent cannabis use or dependence was associated with IQ decline or neurocognitive performance. A study by Meier et al. of co-twins discordant for cannabis use, found little evidence that cannabis use was associated with impaired executive function between, and suggested that family background may explain the lower neurocognitive performance often reported in cannabis users (158). Another group investigated associations

between adolescent cannabis use and IQ and educational attainment and found no association (159). However, without longer follow-up of adolescent cannabis users, whether impairment will emerge later in life is not clear. Additionally, impairment may depend on many factors, such as dose and route of administration, prior exposure, and blood cannabinoid concentrations before and after dosing, which have varied across studies (122).

Maladaptive decision-making has been demonstrated in cannabis users (99–101,128,160,161). In one case, performance below control levels on a reward-based decision-making task was seen in participants who had been abstinent for 25 days (102). Yet, in other studies of impulsive behavior tasks (i.e., Iowa Gambling Task, Go-Stop Task, Monetary Choice Questionnaire, and Balloon Analogue Risk Task (127)) and a monetary risk-taking task (103) current users did not differ from controls. In addition, delay discounting performance did not differ between current and abstinent users and control subjects (103). Thus, whereas acute intoxication by THC appears to increase risky decision-making and sensitivity to reward, the extent to which these effects persist in chronic or abstinent users remains unclear.

The degree of recovery of function with abstinence is a topic of great interest. In a study of adolescents and emergent adults (16–25 years of age), whose abstinence was monitored over 1 month following regular use, improvements were seen in verbal memory, primarily due to improved verbal learning in the first week of abstinence (162). However, cross-sectional studies indicate that effects on attention, verbal and working memory, and psychomotor speed, but not on other cognitive domains, persist in adolescents abstinent for 28 (163) and 35 days (164). Poorer cognitive performance was associated with lifetime cumulative cannabis exposure (163) or an earlier age of onset in adolescents who were abstinent for 30 days (165), and predicted relapse to cannabis use during a 1-year follow-up.

Given the plasticity of the human brain, recovery of function might be expected, and some data support this (166,167), but evidence for persistent cognitive deficits due to cannabis use continues to emerge. Neither the precise metrics of cannabis use required for the persistence of these deficits nor the neural mechanisms underlying them are known. A recent meta-analysis indicated that in addition to small sample size in cross-sectional studies, overlooking effects of abstinence on recovery may falsely magnify the apparent severity and persistence of cognitive deficits associated with cannabis use (168). Future studies monitoring cognitive performance through prolonged periods of abstinence from chronic cannabis use are required to address these pressing questions.

One contributor to the lack of clarity about the effects of cannabis use on cognition may be considerable heterogeneity in the composition of cannabis (169). One relevant study showed greater memory impairment as well as indices of depression and anxiety associated with using cannabis of higher THC content compared to varieties containing lower THC and higher levels of CBD (149). Future research should attempt to quantify the composition of cannabis in prospective studies in order to address this issue.

Therapeutic use of cannabis and its constituents

Preliminary studies of medical marijuana suggest a variety of benefits, including amelioration of chronic pain, inflammation, spasticity, and other conditions commonly seen in physical therapy practice (170). As of December 21, 2018, 756 trials of cannabis were registered on clinicaltrials.gov for evaluation in a variety of conditions, including the following: neuropathic pain, side effects of cancer chemotherapy, schizophrenia, bipolar disorder, major depressive disorder, Tourette syndrome, retinal degeneration, and tinnitus. Practitioners prescribing cannabis are advised to consider the aforementioned cognitive effects, as well as effects on coordination and balance (145,171–173), and on cardiovascular (174,175) and pulmonary function (176,177).

Although evidence suggests that heavy, recreational cannabis use is linked to cognitive deficits and potentially untoward neural changes as outlined above, findings from studies of recreational cannabis use may not be applicable to medical marijuana (178). One study examined whether patients receiving medical marijuana would exhibit improvement in cognitive functioning, perhaps related to primary symptom alleviation (179). The results suggested that these patients experienced improvement in measures of executive functioning, in addition to positive changes in some aspects of quality of life. Few studies beyond this have directly examined the potential impact of medical marijuana on cognitive performance, and further research is needed to clarify the specific neural and cognitive impact of medical marijuana use and how it compares to recreational use.

The ability of cannabinoids to modulate neurotransmission, and to act as anti-inflammatory and antioxidant agents has prompted investigators to evaluate their neuroprotective role in injured brain. Traumatic brain injury and stroke are major causes of death and disability worldwide, with associated long-term cognitive impairment (180,181). The important and complex role of the endocannabinoid system in acute brain injury has led to increasing research in animals and human subjects, suggesting that cannabinoids have an overall positive effect of neuroprotection in acute neuronal injury and that they may enhance neurobehavioral recovery (182–185). Human clinical trials still need to validate these findings and to identify the underlying processes occurring in brain injury.

Numerous clinical trials with constituents of cannabis also are ongoing. As of April 14, 2019, 256 trials of THC are registered with clinicaltrials.gov. Aside from studies evaluating effects of THC on brain activity and various functions, such as memory retrieval and emotional processing, potential effects are being evaluated in chronic pain, bipolar disorder, and improvement of sleep. Dronabinol is FDA-approved to treat patients with Acquired Immune Deficiency Syndrome, who are experiencing anorexia and cachexia, as well as cancer patients who are undergoing chemotherapy and suffer from nausea and vomiting that is resistant to conventional antiemetic treatments. It can be used as tablets in the form of Marinol®, or as Syndros™, an oral solution. Marinol® has been assigned to Schedule III of the Controlled Substances Act, but the DEA maintains FDA-approved products of oral solutions containing dronabinol in Schedule II. Another FDA-approved THC formulation for chemotherapy-induced nausea and vomiting is nabilone (Cesamet®).

One hundred eighty-four trials of the non-intoxicating phytocannabinoid CBD are registered with clinicaltrials.gov for various conditions, including bipolar disorder, substance use disorders, anxiety, heart failure, Sturge-Weber syndrome, and Crohn's disease. Because indications that involve epilepsy and developmental disorders have received substantial attention, we focus on these conditions below. Nabiximols, a 1:1 combination of THC and CBD, is still under study in the U.S. for treatment of chronic cancer pain and muscle spasticity in multiple sclerosis.

Pediatric epilepsy

There is a great need for safe and effective treatment of intractable childhood epilepsy, especially in cases of devastating epileptic encephalopathies, such as infantile spasms, Lennox-Gastaut syndrome (186) and Dravet syndrome (187). In spite of rather limited preclinical data and a lack of well-designed clinical trials, CBD and CBD-enriched whole cannabis plant extracts, have generated enormous interest as potential treatments for epilepsy (188). Following anecdotal reports of potential efficacy from parents who have administered these products to their children (189,190), clinical trials of multiple preparations of CBD were initiated (190–192). The results showed strong efficacy for treatment of Lennox-Gastaut syndrome (193), Dravet syndrome (194), and highly-treatment resistant epilepsy in children and young adults (192), and confirmed reports from open-label studies. Among patients with Dravet syndrome, CBD treatment resulted in a greater reduction in convulsive-seizure frequency than placebo, but was associated with higher rates of adverse events (195). However, accumulating evidence led the U.S. Food and Drug Administration to approve Epidiolex®, a purified CBD-based oral solution, for the treatment of Lennox-Gastaut syndrome and Dravet syndrome on June 26, 2018. Epidiolex® has been assigned to Schedule V of the Controlled Substances Act. Longitudinal prospective studies are required to provide further clarification of the effects of this product in the population intended for its use, especially with respect to the developing brain.

Attention deficit hyperactivity disorder (ADHD)

Although there are no clinical recommendations or systematic research supporting the use of cannabis use ADHD, clinical and anecdotal evidence suggest an increasingly popular perception that cannabis is therapeutic for this disorder (196). Children and adolescents are increasingly being added to medical marijuana registries by their parents for treatment of ADHD and other developmental disorders (197). This practice is occurring despite a dearth of scientific evidence supporting a role for cannabis in ADHD treatment (198). One such study investigated the interaction of ADHD diagnosis and cannabis use in young adults and found no impact on behavioral response inhibition on a Go/NoGo task, but did find that cannabis use was associated with increased signal in the hippocampus and cerebellum during the fMRI Go/NoGo task only in cannabis-using control subjects, but not in cannabis-using ADHD participants (199). The authors suggest this may reflect a delayed maturation trajectory in ADHD participants. Another study found that cannabis use did not exacerbate ADHD-related symptoms (200), but suggested the need for longitudinal neuroimaging studies to investigate the neurodevelopmental cascade that culminates in positive and negative outcomes for those diagnosed with ADHD.

Increased risk for substance use, abuse or dependence of many illicit substances has been well-documented in adolescents and adults with a childhood diagnosis of ADHD, further clouding investigations of the effects of cannabis *per se* on the brain in this patient population (201–203). Among illicit substances used by people with ADHD, cannabis is the most commonly used (203,204), providing opportunities for researchers to design cohort studies on the effects of cannabis in patients with ADHD. Although it is crucial to understand how cannabis use interacts with the neurocognitive vulnerabilities related to ADHD, ethical considerations would preclude assigning pediatric patients with ADHD to receive cannabis in the absence of previous use. Substantial gaps remain in examining neurocognitive and psychiatric outcomes in later life after treatment with cannabis among children and adolescents with ADHD.

Autism spectrum disorder (ASD)

There is increasing interest in cannabinoids, especially CBD as add-on treatment for the core symptoms and comorbidities of autism spectrum disorder (ASD). The endocannabinoid system is often affected in ASD patients with comorbidities, such as seizures, anxiety, cognitive impairments and sleep disturbances (205). Recent findings indicate that anandamide-mediated signaling at CB1 receptors, modulates oxytocin-dependent social reward, suggesting that deficits in the signaling mechanism of anandamide may contribute to social impairment in ASD (206,207). Additionally, epilepsy is common in ASD (20–30%) and more prevalent in individuals with autism-like behavior resulting from particular genetic predispositions, such as Angelman syndrome, Rett syndrome, or Dup15q syndrome (208). In a preclinical study that tested the efficacy of CBD in a mouse model for Dravet syndrome, CBD reduced both seizures and ASD behaviors (209). To date, however, no clinical studies have investigated the effects of any cannabinoid on epilepsy reduction specifically in ASD patients. Further preclinical and clinical studies are needed in order to examine the pros and cons of CBD and other cannabinoids in ASD before they are established as treatment for ASD symptoms and co-morbidities. While all of the medical uses of cannabis mentioned above for pediatric patients with epilepsy, ADHD or autism show merit, care is warranted in taking into account the use of cannabis on the developing adolescent brain. There is little-to-no long-term outcome data on cognition or brain structure in older patients with early-life cannabis exposure for medical intervention.

Conclusion

Decades of research have focused on the impact of recreational cannabis use, documenting decrements across various cognitive domains (e.g., memory, executive function, and likely processing speed), as well as structural and functional brain differences, 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 cannabis use, as adolescence represents a critical period of neurodevelopment, making youth more vulnerable to exogenous influences, including cannabis. 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 cannabis on the brain. It is important, however, to recognize that cannabis is a complex plant comprising 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 of cannabis, 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, which has hindered research efforts.

Current prospective studies on how cannabis exposure can impact brain structure and cognition are beginning to inform public policy, including considerations for age limits and guidelines for use. Nonetheless, additional research is needed to fully understand the impact of marijuana on the brain, especially for medical marijuana where there may be various confounding biological variables unique to individual medical conditions. Extreme care is warranted when evaluating the impact of cannabis on the still-developing adolescent brain. While recreational use among adolescents and early onset users is relatively well studied, a number of areas remain understudied and urgently need data to inform rapidly changing public policy. For example, additional research is needed to clarify the impact of moderate cannabis use, short- and long-term consequences of using high-potency products and novel delivery methods, effects of cannabis use in older adults, and the efficacy and safety of existing products as well as those in development. Additionally, considerations for preclinical models of cannabis inhalation (instead of injection) may facilitate translation of results in the human population.

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Table 1.

Research Questions to be Addressed in Well-designed Studies of How Cannabis use Affects Brain Structure and Function.

	Research Question	Design	Timeframe for Results
1	Does adolescent cannabis use have persistent long-term effects, including enhanced risk for schizophrenia?	1. Retrospective assessment of young adults who report early life use; assess brain metrics and typically confounding factors: education, intelligence, socioeconomic status.	A few years to gather and analyze neuroimaging and cognitive assessments.
		2. Prospective longitudinal design, accounting for confounding variables.	40–50 years; possible alternative is to obtain cognitive or other metrics relevant to neurological integrity before onset of use.
2	Does age of onset of cannabis use determine severity of outcomes; is earlier adolescent use linked to more serious, longer lasting brain changes?	Retrospective and prospective designs in studies of young adults.	A few years to a few decades. Studies investigating this hypothesis are already yielding initial results from retrospective designs.
3	What are the thresholds of frequency of use and dosage beyond which changes to brain structure or cognition become measurable?	Retrospective assessment is challenging, as details regarding use may be unreliable. Legalization should facilitate prospective assessment and objective study design easier.	Short-term outcomes are published. Prospective data are becoming increasingly available from studies that track dosages and frequency of usage; recreational users may feel freeer to discuss usage openly with increasing legalization.
4	Does recreational cannabis use later in life produce long-term effects on brain morphology or cognitive performance?	Older, regular cannabis users can be compared to non-users after a period of abstinence (e.g., 30 days) before cognitive testing. Older adults represent one of the fastest growing usage groups since legalization, making it easier to address this question.	A few years to recruit a population of older, current cannabis users. Usage rates are increasing in this population, including first-time users.
5	How do the medicinal uses of cannabis (and its constituent phytocannabinoids) compare with potential negative effects seen in recreational users?	Observational studies of patient populations who have already been prescribed marijuana. Focus on: 1) older persons, who have higher rates of cancer, pain management problems, nausea, and sleep disturbance to name a few; 2) patents with pediatric epilepsy, who are non-responsive to standard forms of treatment.	A few years to recruit patient populations who taking prescribed marijuana. Dissociating clinical and recreational use will be easier now that full legalization of cannabis use for any purpose negates the need to obfuscate driving factor behind usage
		Randomized, blinded clinical trials of cannabis or its derivatives in conditions where standard medical treatment is ineffective.	Experimental design using cannabis or cannabis-derived compounds is becoming more feasible with the lifting of federal restrictions previously placed on research involving cannabis or cannabis-derived compounds. Medical research should begin to answer many questions regarding efficacy and outcome in the coming years.
6	Does THC actively inhibit the enzyme acetylcholinesterase and prevents aggregation of the amyloid beta peptide?	Studies of participants at greater risk than the general public for subsequent development of Alzheimer's disease, half of whom report current, regular cannabis use.	At least 5 years to recruit a sample of prodromal participants, who use cannabis for a longitudinal study to assess levels of amyloid-p deposition in the brain.