Impact of Adolescent Cannabis Use on Neurocognitive and Brain Development

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KEYWORDS

• Cannabis • Marijuana • Adolescence • Neuropsychological functioning • Memory • Brain development

KEY POINTS

- Converging evidence indicates that ongoing, frequent cannabis use in adolescence is associated with small reductions in neurocognitive functioning.
- Abstinence from cannabis is likely to lead to some recovery in cognitive functioning in adolescents.
- Adolescent-onset, sustained, long-term use of cannabis may result in cognitive deficits that do not recover as readily with abstinence.
- There is some evidence that cannabis use in adolescence is associated with differences in brain structure, but these findings need replication.

INTRODUCTION

There have been substantial shifts in policy and perceptions regarding cannabis use in recent years. In 2018, cannabis was legalized in Canada for individuals 18 years and older. In the United States, cannabis has been legalized for adult recreational use in 18 states and for medical use in 37 states to date. Similar movements toward cannabis legalization and decriminalization have occurred in Europe and Latin America. Concurrent with these trends, societal acceptance of cannabis use has increased, while

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the perception of its harms has decreased.[1] In 2020, 35% of US youth in 12th grade reported cannabis use in the past year, with 6.9% reporting daily or almost daily use.[2] While data indicate that the prevalence of cannabis use among adolescents and young adults has not reliably increased since 2010, daily use has increased in this population.[2,3] At the same time, the availability of cannabis in different forms such as concentrates, oils, and edibles has increased, and the levels of Δ^9-tetrahydrocannabinol (THC), the primary psychoactive ingredient in cannabis, have increased in both flower and concentrate forms.[4,5] Given these changes in cannabis policy and use, there has been considerable interest in research examining health risks of cannabis use, especially in adolescence and young adulthood, when most substance initiation occurs.[6]

This review will summarize the current state of research on associations between adolescent cannabis use, neurocognitive functioning, and brain development. Throughout, the review focuses on a critical question of significant public health importance: are there heightened risks for cognitive and brain development associated with adolescent cannabis use? To address this question, the review first provides critical background information on the neural circuitry involved in cannabis use and the involvement of these systems in neurodevelopment. Next, integrative summaries of research into associations between cannabis use and cognitive functioning, brain structure, and brain functioning will be provided. These summaries will focus primarily on findings in individuals without significant psychopathology (eg, psychosis) or substance use comorbidity (eg, cocaine use), though comorbid mental health symptoms, alcohol use, and nicotine use are very common in these samples. Furthermore, where possible, this review will highlight findings from large, representative studies; meta-analyses; twin and family studies; and longitudinal studies. As discussed below, cross-sectional studies with small, selective samples are more likely to lead to imprecise estimates of any potential true effect, resulting in lower replicability of findings and the potential for both false positive and false negative results,[7] especially with the smaller effect sizes expected in neuroimaging and neuropsychological research into cannabis use for example,.[8,9] Larger studies, meta-analyses, longitudinal research, and twin and family studies can minimize problems with reduced statistical power and help resolve discrepancies and confounds often encountered in smaller, cross-sectional studies. Finally, we conclude with an overview of findings, limitations of the current literature, future directions, and clinical care points related to this body of research.

Neurocircuitry of Cannabis

The psychoactive effects of cannabis are primarily driven by Δ^9-THC, one of at least 85 cannabinoids in *Cannabis sativa* discovered to date.[10] Cannabinoids bind with specific G-protein-coupled receptors known as cannabinoid receptors (CB-Rs). Two primary CB-Rs have been well characterized to date—CB_1 and CB_2. CB_1 receptors are primarily found in the central nervous system, with a high density in the basal ganglia, hippocampus, limbic system, and cerebellum.[11,12] CB_2 receptors are mainly found in peripheral tissue, particularly in the immune system. Endocannabinoids, such as anandamide and 2-arachidonoylglycerol, are naturally occurring ligands that activate CB-Rs. The endocannabinoids, CB-Rs, and enzymes responsible for the synthesis and degradation of endocannabinoids together comprise the endogenous (endocannabinoid [eCB]) system. CB_1 receptors in the brain have a wide role in maintaining neuronal inhibitory and excitatory balance via the regulation of neurotransmitter release and synaptic plasticity, especially glutamate and gamma-aminobutyric acid (GABA).[13] THC mimics endocannabinoids and primarily binds to CB_1 receptors in

the brain, but its effects are more prolonged than those of endocannabinoids. Thus, THC seems to disrupt the regulatory roles of the eCB system and produces the behavioral, cognitive, memory, and motor effects of cannabis intoxication.

The eCB system is expressed early in brain development,[14] and animal and human studies suggest that the activity of endocannabinoids and CB-Rs may reach its peak during puberty.[15] Moreover, extensive research in the last 20 years has shown that the eCB system is critical to multiple neurodevelopmental processes from the early postnatal period through adolescence.[16,17] These processes include neuronal development and specification early in brain development, as well as neurogenesis, synaptic pruning, and white matter development during adolescence.[18,19] As such, the eCB system contributes to the development of efficient communication within and between brain networks during adolescence, including the establishment of adaptive cognitive functioning and emotion processing.

Adolescence as a Critical Neurodevelopmental Period

Adolescence is a period of dynamic neurobiological and behavioral changes. There are substantial increases in cognitive capacities, particularly in working memory, cognitive control, self-regulation, and abstraction.[20] Relatedly, marked neurodevelopmental changes occur during adolescence, including increased myelination, synaptic pruning, and increases in white matter development, with notable maturation of prefrontal regions and associated neural circuitry that proceeds into the mid-20s.[21–23] Because of this prolonged neurodevelopmental period, and the potential involvement of the endocannabinoid system in such brain-behavior changes, concerns have been raised regarding whether the use of cannabis during this "critical period" may disrupt normal trajectories of brain, emotional, and cognitive development.[15,24,25]

Preclinical studies have supported the biological plausibility of this hypothesis. Rodents at ages approximating adolescence have shown specific vulnerabilities to repeated exposure to THC or CB-R agonists compared with adult rodents.[26,27] Such studies have shown behavioral deficits in working memory and learning, reduced activity at synapses, and structural changes in the hippocampus with cannabinoid administration during adolescence, while few deficits appear with administration during periods approximating adulthood in rodents.[28,29] Interestingly, studies have shown some of these deficits to be reversible after short periods of abstinence.[30,31] Thus, evidence from animal models supports heightened adolescent vulnerability to cannabis exposure, with some behavioral deficits potentially reversible with abstinence.

Challenges of Evaluating Research Regarding Cannabis Use

Before reviewing the state of research on cannabis, cognitive functioning, and brain development, it is important to contextualize the challenges of research into the causal effects of cannabis use, as well as exposure research more broadly. Randomized controlled trials are the gold standard of evidence in determining causality. As randomized controlled trials of longer-term cannabis use are not feasible with adolescents because of legal, ethical, and safety concerns, studies examining the residual effects of cannabis are observational, and many use between-subject designs. Observational studies of exposures that individuals select, such as substance use, may create selection biases and present difficulty in removing the influence of confounding factors that may be associated both with the exposure and outcomes of interest. Such confounders have the potential to create spurious associations between cannabis and cognitive or brain outcomes, especially when effect sizes for exposure are modest. For example, frequent cannabis users have been shown to have greater alcohol use, other substance use, and tobacco use[32]; personality traits that increase the

risk for frequent substance use[33]; lower socioeconomic status[34]; higher trauma and adverse event exposure[35]; and more mental health comorbidities[36] than nonusers or occasional cannabis users. All of these factors have also been reported as associated with cognitive and brain development, and several are often difficult to resolve temporally in relation to cannabis use, including some that have been shown to predict cannabis initiation.[37] Alternatively, one could study cannabis users without these confounds to better isolate effects of cannabis, but the results are likely not generalizable to a typical population of frequent cannabis users (who are likely to have these other relevant factors), reducing the potential generalizability and impact of findings. Thus, studying cannabis in the "real world" and using proper frameworks and assumptions for modeling variables of interest is required. Without proper modeling of predictors, outcomes, and confounders, including the consideration of which variables should and should not be statistically controlled, it is challenging to rule out potential alternative explanations for findings and conduct effective causal inference.[38] Indeed, reducing the likelihood of alternative explanations for findings potentially caused by cannabis use will contribute to converging lines of evidence and inform public perception and policy related to cannabis.

As detailed below, there are also challenges in interpreting the published research on cannabis, cognitive functioning, and brain development due to substantial heterogeneity in methods, measurement, and sample characteristics. Continuous measures of cannabis use are rarely used due to difficulties in accurately measuring the amount or frequency of use (which is usually collected retrospectively), and heterogeneity is inevitably introduced by the different phenotypes (ie, operationalizations of grouping variables) used across studies. For example, studies of adolescent cannabis users have examined individuals diagnosed with a cannabis use disorder, daily cannabis users, regular cannabis users, those who have used cannabis a certain number of times, or those who initiated cannabis use before a particular age. There is likely to be substantial variability between and within these phenotypes in cannabis use frequency/intensity, as well as confounders, which may lead to noisy data. Furthermore, researchers sometimes explore more than one of these phenotypes as predictors but may only highlight the phenotype with significant findings. There are efforts underway to harmonize data collection related to cannabis,[39,40] but they have not been applied consistently to date. There are also persistent questions around variability in the selection, analysis, and reporting of neurocognitive data,[41,42] including publication bias, as well as analytical flexibility in neuroimaging studies.[43,44] Such "forking paths" are common in these studies and likely to affect the replicability of results.[45]

Highlighting the challenges in interpreting this line of research does not necessarily impede one's ability to come to informed conclusions about the risks of cannabis for cognitive and brain development. However, these data are complex, and it is beneficial to develop systematic approaches to interpretation, including the consideration of converging lines of replicable evidence. Readers should keep these critiques in mind when evaluating research in this area, including questions about variables of interest, measurement error, and causal conclusions.

RESIDUAL EFFECTS – COGNITIVE FUNCTIONING

Studies examining the relationship between cognitive functioning and problematic cannabis use in human adolescents have increased substantially over the past 2 decades. There is now a broad consensus that during acute cannabis intoxication, deficits in attention, executive functioning, and memory are evident,[46,47] though effects may differ for frequent cannabis users.[48,49] However, residual cognitive effects (ie,

those persisting after episodes of acute intoxication) are still debated, especially after periods of abstinence from cannabis use.

There are several possible hypotheses regarding adolescent cannabis use and residual effects on cognitive functioning. The first is that cannabis use is associated with cognitive deficits that are caused by cannabis-associated neurotoxicity and are likely not reversible. If this hypothesis is true, abstinence from cannabis or reductions in cannabis use is unlikely to result in the amelioration of cognitive deficits. Of note, if this hypothesis is true, there are several additional questions regarding the dose of cannabis and timing of cannabis initiation that would be sufficient to cause such a decline. The second hypothesis is that cannabis is associated with cognitive deficits, but that these deficits are more associated with residual or withdrawal effects as opposed to neurotoxicity. If this hypothesis is true, cognitive deficits will be reversible with reductions in or abstinence from cannabis use. A third hypothesis is that any cognitive deficits observed in cannabis users are confounded by other correlated factors or due to preuse factors that would have caused deficits even in the absence of cannabis use. Of note, these hypotheses are not mutually exclusive, as deficits could be due to correlated or preuse factors *and* to cannabis itself, and some cognitive deficits may abate with abstinence while others persist.

Cross-Sectional Studies

Some of the early cross-sectional studies in adolescents and young adults reported relationships between heavy, frequent, or problematic cannabis use and poorer cognitive functioning, including executive functioning and reasoning, attention, speed of processing, and episodic learning and memory.[50–53] Relationships between earlier initiation of cannabis use and increased cognitive deficits were also reported.[54–56] Moreover, some studies showed dose-dependent effects of cannabis on cognitive functioning, such that individuals with more occasional use patterns (eg, once per week or less) display relatively intact cognitive functioning, while those with more frequent use or cannabis use disorders show impaired cognitive functioning.[51] However, most of these studies had small samples and were likely underpowered given the expected small-to-moderate cognitive effects associated with frequent cannabis use.[7]

Larger cross-sectional studies of community-based samples and meta-analyses have suggested greater complexity in findings related to cognitive functioning in adolescent cannabis users. For example, in a large community-based sample of adolescents and young adults (ages 14–21) from the Philadelphia Neurodevelopmental Cohort (PNC), Scott and colleagues[57] examined cognitive functioning in 227 past-year frequent cannabis users (2–3 times per week or more) and 940 past-year occasional cannabis users (1–2 times per week or less). Occasional cannabis users did not evidence cognitive deficits compared with nonusers and actually performed slightly better in certain cognitive domains. Moreover, the study found limited cognitive deficits in frequent cannabis users across the whole age range of the sample. However, they did find an interaction between age and cannabis use, such that frequent cannabis users at younger ages (14–17) performed worse in executive functioning than nonusers.

Meta-analyses quantitatively synthesize results of multiple studies and can estimate the magnitude of effect sizes (eg, cognitive test scores) and whether explanatory variables affect variability in outcomes across an existing literature. Meta-analyses can also address inconsistencies across a research literature by standardizing outcomes and reducing the impact of varying statistical power. One meta-analysis of cross-sectional studies examining cognitive functioning in adolescent and young adult cannabis users (up to age 26) has been conducted to date. This study found

differences of a small magnitude (Cohen's *d* 0.21–0.33) between frequent cannabis users and nonusers in episodic learning and memory, executive functioning (cognitive flexibility, inhibition, and working memory), speed of processing, and attention.[9] These effect sizes and their relative magnitude across cognitive domains were similar to results from prior meta-analyses of adults.[58,59] However, several additional analyses highlighted the complexity of findings. First, neither age at first use nor the overall age of the sample in each study had a significant effect on the magnitude of the effect sizes. Second, studies of treatment-seeking individuals had larger magnitude of cognitive effects than studies of community samples. Finally, abstinence impacted the magnitude of effect sizes. Increasing length of abstinence—both the amount required by a study and the mean length reported by participants in a study—was associated with a smaller magnitude of effect sizes. In addition, studies that required an abstinence period from cannabis use of longer than 72 hours (corresponding to the postpeak period for most cannabis withdrawal symptoms[60]) had a very small, nonsignificant effect size. Together, these results support small reductions in specific neurocognitive domains with continuing cannabis use in adolescents and young adults but also raise uncertainty about the persistence of cannabis-associated cognitive alterations after periods of abstinence.

Longitudinal and Twin Studies

Cross-sectional research designs allow minimal causal inferences and cannot determine whether cognitive deficits were present before cannabis use or might be accounted for by other confounders. Unlike cross-sectional studies, longitudinal designs can examine trajectories of change and temporal relationships between variables of interest and may be able to explore whether preuse risk factors are distinct from the consequences of cannabis use. For instance, several studies have shown that adolescents at risk of developing problematic cannabis use display preuse cognitive vulnerabilities, such as deficits in working memory and inhibitory control,[61–64] which may place such individuals at greater risk of earlier and more frequent substance use[65–67] and confound interpretation of cognitive data. Consideration of such confounders is critical for the interpretation of observational longitudinal data.

Smaller longitudinal studies have linked continued cannabis use in adolescence to cognitive decline in processing speed, executive functions, and episodic memory.[61,68–70] However, similar to results from meta-analyses, deficits improve with verified abstinence over a period of weeks,[71,72] and cannabis abstinent adolescents and young adults often perform similarly to nonusers.[52,73–77]

Perhaps the strongest evidence for cannabis-associated cognitive deficits comes from analysis of the large Dunedin Longitudinal Study by Meier and colleagues.[78] In a landmark study of 1037 individuals followed from childhood to age 38, intelligent quotient (IQ) data were examined from individuals in childhood (before any cannabis use had occurred) and again at age 38. The authors showed that individuals who started using cannabis at least weekly by age 18 and continued using cannabis almost daily throughout early adulthood showed significant declines in IQ (especially on verbal IQ measures) between childhood and age 38, corresponding to approximately 6 IQ points. Moreover, individuals who used infrequently at age 38 still showed IQ decline if they used weekly before age 18, but those who did not initiate regular cannabis use before age 18 did not show decline if they had reduced their use by age 38. In other words, abstinence seemed to improve cognitive functioning in those who delayed the initiation of frequent cannabis use until after age 18. Of note, the authors found mostly similar results after adjusting for several other confounders, including other substance use, psychopathology, and recent cannabis use.

Additional work has extended these results in large cohort studies with longitudinal measurements of cognitive functioning. Mokrysz and colleagues[79] examined IQ data at age 15 after controlling for childhood IQ at age 8 in 2235 adolescents from the Avon Longitudinal Study of Parents and Children (ALSPAC). They found that cumulative cannabis use was negatively associated with IQ at age 15, and those who reported using cannabis 50 or more times had IQs that were almost 3 points lower than nonusers. However, when analyses controlled for several confounders, including adolescent cigarette, alcohol, and other substance use, any relationships between cumulative cannabis use and IQ were attenuated, indicating significant complexity in these relationships. In another study of 3232 individuals from the ALSPAC cohort, Mahedy and colleagues[80] found that early-onset regular cannabis use between ages 13 and 18 was associated with poorer working memory and response inhibition at age 24 compared with nonusers, even after controlling for socioeconomic status. However, analyses that attempted to examine causality in these relationships using Mendelian randomization[81] were inconclusive. Morin and colleagues[64] examined associations between cannabis, alcohol, and cognitive functioning in a unique dataset that repeatedly measured cognition and substance use between 7th and 10th grade in 3826 adolescents from Montreal, Canada. They used multilevel models to explore how changes in one variable (eg, cannabis use) were associated with changes in another (eg, working memory performance) over time by examining concurrent and time-lagged associations between variables. They found that the use of cannabis and alcohol were both associated with lower working memory, perceptual reasoning, and inhibitory control. Furthermore, they reported that cannabis was associated with episodic memory performance, but only transiently (potentially abating with abstinence). Finally, they found that cannabis use was associated with time-lagged effects on inhibitory control even after controlling for alcohol use. This finding was interpreted as potentially consistent with a neurotoxic effect of cannabis, though there was limited discussion of the magnitude of the effect or its potential clinical significance.

Several studies have taken advantage of informative cotwin control designs to help determine whether associations between cannabis use and cognitive functioning are confounded by genetic and family environment influences. In such studies, examining differences in cognitive functioning or decline between cannabis-exposed twins and their nonusing (or abstinent) siblings can help determine the feasibility of a causal association between cannabis use and cognitive functioning by accounting for unmeasured influences that are common for twin pairs and could also be associated with cognitive functioning.

In a large sample that combined 2 longitudinal population-based cohorts of twins, including 789 from Los Angeles and 2277 from Minnesota, Jackson and colleagues[82] examined change in 4 subtests of IQ from before cannabis initiation to the late teens. Of the four subtests, a measure assessing vocabulary knowledge showed an approximately 4-point decline in those who used cannabis during the follow-up period; unexpectedly, however, no relationship was found between cannabis frequency and IQ decline within the group of users. Furthermore, in a series of cotwin analyses, there was minimal evidence for greater IQ decline in twins who used cannabis (even frequently) compared with their nonusing twins. Similarly, in a longitudinal sample of 2232 British twins, Meier and colleagues[63] examined potential neuropsychological decline from age 12 to 18 by cannabis use. Adolescents who were dependent on cannabis at age 18 were found to have lower IQ at all timepoints (including before cannabis initiation), but cannabis dependence was not associated with IQ decline from age 12 to 18. Moreover, twins discordant for cannabis use showed minimal evidence of greater IQ decline or reductions in executive functioning compared with their

cotwins. In a sample of 856 adolescent and young adult twins from Colorado, Ross and colleagues[83] used a cotwin design to examine associations between cannabis use, intelligence, and a well-validated battery of executive functioning measures. Overall, there was minimal evidence for associations between cannabis use and either intelligence or executive functioning after accounting for other substance use and within-family effects. In contrast to these studies, Ellingson and colleagues[84] recently found associations between cannabis use and memory using sibling-comparison analyses (not twins) that attempted to control for shared family effects. In a sample of 1192 adolescents drawn from substance abuse treatment programs, alternative schools, and juvenile probation departments in the US, cognitive functioning was assessed during adolescence (mean age 17.1–17.6) and young adulthood (mean age 23.5–23.8). In contrast to prior research, the authors reported minimal associations between cannabis use and cognitive functioning during adolescence. However, there were associations between the age of onset of regular cannabis use and verbal memory during young adulthood. Of note, there were no significant associations between cannabis use and measures of IQ or executive functioning at any timepoints.

There are 2 limitations to note regarding twin studies of cannabis use. First, despite the strength of this design to disentangle complex associations, most twin studies have had small numbers of frequent cannabis users and even fewer numbers of twins discordant for cannabis use. Second, no twin studies have examined these relationships over periods as long as Meier and colleagues,[78] and it is possible that cannabis-associated effects could emerge over longer periods.

Summary – Cannabis and Cognitive Functioning

Cross-sectional studies suggest cognitive reductions of a small magnitude in episodic memory, executive functioning, attention, and processing speed in adolescents who frequently use cannabis, especially in those who are treatment-seeking. However, abstinence from cannabis is associated with the attenuation of these reductions. Longitudinal studies are somewhat inconsistent but indicate that early and continued use of cannabis for longer periods of time (perhaps >10 years) may be associated with sustained cognitive decline, even with abstinence. Twin studies have challenged causal associations between cannabis and cognitive functioning in adolescence, suggesting that cognitive dysfunction might be associated with familial or shared environmental factors as opposed to cannabis-specific effects.

RESIDUAL EFFECTS – BRAIN STRUCTURE

Cross-Sectional Studies

Magnetic resonance imaging (MRI) studies in adolescents and young adults have examined differences between regular cannabis users and nonusers in several measures of brain structure, including volume of specific brain regions, thickness of the cerebral cortex, and density of brain gray matter. Early studies mostly used region of interest approaches to focus on brain regions with high densities of CB_1 receptors,[85] including subcortical structures such as the basal ganglia, hippocampus, and amygdala, as well as the cerebellum, cingulate cortex, and prefrontal cortex. However, consistent findings from initial studies in this area have been somewhat elusive, partially due to small sample sizes and variability in methodology.

Several cross-sectional studies found frequent cannabis use in adolescents and young adults was associated with smaller hippocampal volumes,[86–88] though other studies failed to replicate these differences.[89–92] Inconsistent results from cross-sectional studies were also reported in amygdala, striatum, cerebellum, orbitofrontal

cortex, and cingulate cortex,[86,89,91,93–98] despite a high density of CB_1 receptors in these regions. Similarly, adolescent frequent cannabis users have been reported to have thinner prefrontal cortex compared with nonusers,[91,99] although several studies have not replicated these findings or have even found *thicker* prefrontal cortex in cannabis users.[90,100,101]

Larger cross-sectional studies have generally shown fewer consistent reductions in volume and cortical thickness in adolescent and young adult cannabis users. Weiland and colleagues[102] found no differences in measurements of subcortical volume, shape, or surface area in a sample of 50 adolescent daily cannabis users compared with nonusers. Similarly, in a sample of 439 adolescents, including 201 with weekly or greater cannabis frequency, Thayer and colleagues[103] found no associations between days of cannabis use in the prior 30 days and gray matter volumes, even when analyses were restricted to the sample of weekly users. In a sample of adolescents and young adults from the PNC, Scott and colleagues[104] found little evidence of dose–response relationships between cannabis use and brain volumes, cortical thickness, or gray matter density, and no age by group interactions suggesting adolescent vulnerability. One unique study examined links between cannabis use in adolescence, cortical thickness, and risk of schizophrenia by leveraging 3 large, population-based samples. French and colleagues[105] examined cortical thickness in 1574 participants between 12 and 21 years old and found a negative association between cannabis use by age 16 and cortical thickness, but only in men with a high polygenic risk score for schizophrenia (as determined by 108 genetic loci that had been identified at the time). The authors suggested that cortical thinning may mediate the link between cannabis use and risk of schizophrenia in men.

Two meta-analyses of cross-sectional structural neuroimaging studies in adolescent and young adult cannabis users have been conducted to date. A recent meta-analysis focused specifically on studies of cannabis users between 12 and 21 years old that used whole-brain voxel-based morphometry and voxelwise analyses to examine brain gray matter volume.[106] Unfortunately, this only included 6 total studies for meta-analysis. The authors reported that there were no significant differences between cannabis users and nonuser comparison groups when they synthesized results across studies. However, in follow-up meta-regressions, one region, the left superior temporal cortex, showed an increasing magnitude of differences between groups with age (ie, smaller volumes), suggesting a potential developmental gradient of cannabis associations. However, as the authors stated, as these results were not observed in primary analyses and were based on only 6 studies, they should be treated with caution. In a separate meta-analysis of volumetric structural neuroimaging findings associated with regular cannabis use, studies of adolescents and young adults comprised at least half of the 30 studies included.[8] Interestingly, findings synthesized from these cross-sectional studies suggested differences in hippocampal and orbitofrontal cortex volumes of a small magnitude in regular cannabis users, but minimal differences in other regions or in overall gray matter, white matter, or whole-brain volumes.

Longitudinal and Twin Studies

There have been few longitudinal studies of changes in brain structure associated with adolescent cannabis use or neuroimaging studies of twins discordant for cannabis use. However, such studies are crucial to increasing understanding of the potential impact of cannabis use on neurodevelopment, as shared familial factors may explain some brain structural differences seen in cannabis users[107] and some structural brain differences may predate and predict regular cannabis use. For example, several

studies have shown that reduced volume of the orbitofrontal cortex is predictive of cannabis use during adolescence,[108–110] highlighting challenges in the interpretation of cross-sectional findings.

Longitudinal structural neuroimaging studies with small samples of adolescent cannabis users have shown conflicting findings. A study of 20 young adult heavy cannabis users found no structural differences in the hippocampus at either baseline or after approximately 3 years of cannabis use.[111] A 3-year longitudinal study of adolescent cannabis and alcohol users found reduced thinning of the cortex (ie, thicker cortex) in prefrontal, parietal, temporal, and occipital cortex, with greater cumulative marijuana use associated with increased thickness in temporal cortex at the follow-up visit.[101] Similarly, a small study of adolescent cannabis users followed over 18 months showed reduced levels of cortical thinning (ie, thicker cortex) in prefrontal, temporal, and parietal regions.[112] In contrast to findings of diminished cortical thickness from smaller studies, a recent, large-scale longitudinal study of 799 adolescents from the community-based IMAGEN cohort found that lifetime cannabis use was associated with *accelerated* cortical thinning from ages 14 to 19 in bilateral prefrontal cortex.[113] The regions that showed associations with cannabis use were also regions likely to show neurodevelopmental changes with age, providing some evidence for cannabis-associated changes in networks exhibiting protracted maturational trajectories.

Few studies have examined longer-term trajectories of brain structure in adolescent cannabis users. Using data from the Pittsburgh Youth Study, Meier and colleagues[114] used latent class growth analysis to identify different trajectories of adolescent cannabis use based on the annual assessments of cannabis use from ages 13 to 19 (n = 181). Despite identifying 4 trajectories of cannabis use during adolescence, they found no differences by a trajectory in cortical thickness, cortical volumes, or subcortical volumes when MRIs were acquired between ages 30 and 36.

To date, 2 cotwin studies have examined associations between cannabis use and brain structure in adolescence. In a sample of 436 young adult twins, Harper and colleagues[115] collected dimensional measures of cannabis use and alcohol use and examined their association with cortical thickness in specific networks of the brain that underly functional systems of executive control and salience, including several regions in the prefrontal cortex. There were significant associations between alcohol abuse and reduced cortical thickness within these networks, and cotwin analyses indicated that these associations potentially reflected both familial factors and effects attributable to alcohol. However, there were no associations between cannabis and cortical thickness. Interestingly, in the same sample of twins, Harper and colleagues[116] found that alcohol use disorder and cannabis use disorder were both associated with reduced thickness of the medial (but not lateral) orbitofrontal cortex. Analyses of twins discordant for alcohol and cannabis use indicated that reductions in the medial orbitofrontal cortex seemed to be associated with both familial risk and substance effects.

Summary – Cannabis and Brain Structure

There is some initial evidence for alterations in the structure of the hippocampus and prefrontal cortex associated with cannabis use during adolescence, but significant heterogeneity exists in studies to date. Furthermore, some large-scale longitudinal research suggests that these structural brain changes are linked with cumulative cannabis use, but twin studies suggest that familial factors may contribute to brain changes associated with cannabis use. More prospective longitudinal studies and genetically informed designs are needed to assess the specific contribution of

cannabis to structural brain alterations in adolescent cannabis users. Such studies are especially critical to disentangle substance-specific associations, as several different substances seem to share general associations with structural brain measures [117]

RESIDUAL EFFECTS – BRAIN FUNCTION

Several studies have examined potential differences in functional brain activation in adolescent frequent cannabis users using data collected during cognitive or emotional tasks (ie, task-based fMRI) or during rest (ie, resting-state fMRI). Several prior reviews have summarized these studies, and most have concluded that cannabis use during adolescence is associated with functional brain alterations[25].[118–120] Yet, most findings are from small studies, and there is substantial inconsistency.

Early fMRI studies primarily used task-based approaches with small samples of adolescent cannabis users. Most studies found increased fMRI activation in "task positive" brain networks in adolescent cannabis users. For example, studies of working memory tasks have primarily reported increased prefrontal activation in adolescent cannabis users, despite showing equivalent task performance.[121–123] Similarly, 2 studies have reported increases in activation in prefrontal control networks associated with adolescent cannabis use during a task of response inhibition,[124,125] though another showed minimal group differences in fMRI during inhibition.[126] However, the interpretation of these data is not straightforward. To this end, studies of normative neurodevelopment have shown that "task positive" fMRI activation in the frontoparietal executive control network (FPN) during executive control tasks (eg, working memory and response inhibition) are associated with increasing age across development and improved task performance.[23,127] Thus, it is challenging to interpret increased activation in the FPN (whereby most of the reported activations would be localized) as reflecting abnormalities, as greater activation is consistently associated with better cognitive functioning in normative development. Larger studies with links between brain and behavior are needed to resolve this discrepancy.

There have also been fMRI studies of reward processing and emotion processing focusing on adolescent cannabis users. Studies of reward processing in adolescent cannabis users have not produced consistent findings to date.[128,129] However, a large study using an affective face processing task showed greater amygdala reactivity to angry faces in adolescent cannabis users, suggesting potential hypersensitivity to threat associated with cannabis.[130] Moreover, a follow-up study in the same cohort indicated that right amygdala hyperactivity to angry faces at baseline was a predictor of cannabis use (but not alcohol use) 5 years later, even in those who had not used cannabis at baseline.[131] These findings are intriguing and deserve replication and extension.

Two meta-analyses of the fMRI literature have been conducted to date but offer limited results. Blest-Hopley and colleagues[132] were only able to include 7 studies of adolescent cannabis users in a meta-analysis of whole-brain fMRI studies, finding significantly greater activation in adolescent cannabis users in the right inferior parietal gyrus and right putamen. In a separate meta-analysis, Blest-Hopley colleagues[133] only found 3 fMRI studies of adolescent cannabis users in which they acquired functional MRI data after 25 days of abstinence. Synthesizing results from these 3 studies suggested increased fMRI activation in abstinent adolescent cannabis users in regions of the dorsolateral and ventrolateral prefrontal and posterior parietal cortices, most of which are part of the FPN. However, as noted by the authors, all 3 articles were from the same laboratory and had some degree of overlapping samples, suggesting that the consistency of findings may be inflated.

Longitudinal and Twin Studies

In adolescent cannabis users, there have been no fMRI twin studies and only one longitudinal fMRI study. One small study (22 treatment-seeking adolescents with cannabis use disorder) reported decreased connectivity between caudal anterior cingulate cortex and dorsolateral and orbitofrontal cortices in adolescent cannabis users across 18 months.[134] Longitudinal changes in fMRI activation by cannabis use trajectories await further study.

Summary – Cannabis and Brain Function

There are relatively consistent findings from small studies of increased activation in "task positive" regions of the FPN in adolescent cannabis users, but the straightforward interpretation of these data is challenging. Unfortunately, fMRI research on adolescent cannabis use is subject to the same limitations as the cognitive and structural MRI research discussed above. As such, most fMRI studies in adolescent cannabis users have had small sample sizes, and many have included cannabis users with significant alcohol use, creating difficulties in the separation of risk factors. Some have not addressed issues of abstinence, which can impact measures of brain functioning.[123,135] As always, whether potential differences in fMRI measures are due to cannabis exposure is challenging to evaluate. For example, several studies have found that fMRI measures predict the initiation of cannabis use or problematic cannabis use during adolescence, including activation in regions of the FPN that overlap with those associated with cannabis use in cross-sectional studies.[37,136] Clearly, longitudinal research in larger samples is needed to replicate and expand on prior fMRI results.

SUMMARY

A substantial literature examining risks of adolescent cannabis use for brain and cognitive outcomes has amassed in the past 2 decades, but there is considerable heterogeneity in this research. Studies differ in the timeframe of measurements, frequency of use, measurements of cannabis quantity, types of cannabis used, and measures to assess neurocognitive functioning, brain structure, and brain functioning. This heterogeneity, combined with potential confounding and selection bias inherent in substance use research, has created challenges in interpreting this literature and reaching informed conclusions. However, at this point, several conclusions are warranted.

First, there is relatively consistent evidence that ongoing, frequent cannabis use is associated with small magnitude reductions in cognitive functioning. The clinical significance of these reductions is underexplored, as few studies have explored how such reductions are associated with functional outcomes.[61,78] However, an argument could be made that any reductions in cognitive functioning during continued periods of neurodevelopment are concerning from a public health standpoint. Moreover, even if adolescents eventually cease use, there is some evidence that frequent cannabis use during adolescence could reduce educational attainment[137] which could have downstream effects on occupational attainment and income.[138] Nonetheless, more research is needed to explore links between cannabis-associated cognitive deficits in adolescence and future educational, occupational, and psychosocial outcomes.

Second, there is relatively consistent evidence that abstinence is associated with improved cognitive functioning in cannabis users. The magnitude of this improvement is potentially dependent on the age at cannabis initiation and length of frequent cannabis use, although more research is needed to understand how these factors impact the recovery of function. In some cases, abstinence decreases the magnitude of reductions to levels that are indistinguishable from those of nonusers. However,

achieving abstinence is challenging in individuals with cannabis dependence,[139] especially in individuals who establish patterns of frequent cannabis use in adolescence.[140] Thus, while it is potentially encouraging that abstinence may improve cognitive differences between cannabis users and nonusers, many adolescent-onset users are not able to achieve sustained abstinence.

Third, studies with longer follow-up periods (ie, >10 years) and with participants with the greatest cannabis frequency tend to show the strongest evidence of cannabis-related cognitive or IQ decline, while studies with shorter follow-up periods or lesser cannabis use tend to show limited associations after accounting for confounding factors, familial or genetic influences, and abstinence. This pattern is consistent with the hypothesis that cannabis-linked cognitive *impairments* after a period of abstinence are more likely to be evident after years of heavy cannabis use as opposed to shorter periods of regular use.[141]

Fourth, there are cognitive, brain structure, and brain activation differences (among other relevant factors) that seem to predict cannabis initiation/escalation or problematic substance use in general. These factors make straightforward interpretation of results challenging in this field. They also stress the need for multiple informative designs to triangulate evidence regarding the relationship between cannabis use in adolescence and brain-behavior functioning.

Finally, despite relevant mechanistic models and preclinical data, suggesting adolescent vulnerability to the brain effects of cannabis, there is mixed evidence for this vulnerability in humans to date. To this end, meta-analyses indicate that the magnitudes of neurocognitive effect sizes are remarkably similar in adult and adolescent frequent cannabis users. There are also limitations in research designs that attempt to examine heightened adolescent vulnerability to cannabis. Comparisons between early- and late-onset users are inconsistent in their definitions of early onset, and earlier age of onset is often associated with longer duration of use and heavier cannabis use,[61] creating challenges in isolating this effect. However, there is evidence from one rigorous longer-term longitudinal study of increased risk for poor cognitive functioning outcomes for those who initiate regular use in adolescence (compared with initiating use after age 18) and continue consistently using throughout adulthood.

Regardless of conclusions about cognitive and brain health, frequent cannabis use during adolescence is risky. This is especially true given the many unknowns left to discover with cannabis and the changing landscape of cannabis products available. There is also substantial variability in associations between cannabis and cognitive functioning; even with smaller effect sizes, frequent and prolonged cannabis use in adolescence may place certain vulnerable individuals at heightened risk of poor brain and behavior outcomes. Moreover, there are multiple pathways through which cannabis could influence health, and regular cannabis use during adolescence has been associated with several functionally relevant risks that are not discussed here, including increased likelihood of cannabis use disorder, increased risk for psychosis and schizophrenia, risks for poorer academic and occupational outcomes, and worsening of mental health conditions. These risks, in combination with potential risks for cognitive and brain functioning, highlight the potential benefits of delaying regular use of cannabis until early adulthood. Recommendations to adolescents from clinical providers and public health messengers should focus on such evidence-based assessments of risks.

Future Directions

While there has been substantial progress in studying cannabis use in adolescents over the past 2 decades, there are several areas of future research and development

that are needed. There has been limited work to date regarding the chronic impact of different levels of THC or other cannabinoids on cognitive functioning, despite some data suggesting differential acute effects depending on cannabinoid constituents.[142,143] In addition, the literature on "synthetic cannabinoids" (eg, K2) is very limited at this time, and future work will need to examine how these substances may impact brain and cognitive functioning. There is also likely substantial variability in risk for brain-behavior problems associated with cannabis, and research into patient factors (eg, genomics) that may lead to adverse outcomes will be critical. Data from large-scale, population-representative studies will be essential to resolve many of the discrepancies described above and propel understanding of vulnerability in cannabis-associated brain-behavior effects. In the United States, the Adolescent Brain Cognitive Development study (https://abcdstudy.org) is acquiring repeated cognitive, mental health, and neuroimaging data on 10,000 adolescents starting from age 9 or 10, which will provide substantial data to answer critical questions about the risks of cannabis use in adolescence.

CLINICS CARE POINTS

- Frequent, active cannabis use in adolescents may be associated with small magnitude cognitive deficits in memory, attention, executive functioning, and speed of processing
- Adolescents who are frequent cannabis users are also likely to have psychiatric and substance use comorbidities that contribute to identified cognitive deficits
- Large magnitude cognitive deficits are less likely to be attributable to cannabis use
- Occasional cannabis use in adolescents is less likely to be associated with cognitive deficits except during the period in which an individual is intoxicated
- Abstinence from cannabis is likely to lead to some recovery in cognitive functioning
- Adolescent-onset, sustained, long-term use of cannabis may result in cognitive deficits that do not recover as readily with abstinence
- There are clear potential benefits of delaying regular use of cannabis until after the age of 18

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