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Neurodevelopmental Effects of Cannabis Use in Adolescents and Emerging Adults with ADHD: A Systematic Review

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Abstract

Objective: Systematically review the scientific literature to characterize the effects of cannabis use on brain structure, function, and neurodevelopmental outcomes in adolescents and young adults with ADHD.

Method: Systematic review following PRISMA guidelines utilizing PubMed, Embase, PsycINFO, and Cochrane CENTRAL trials register from inception until 1 January 2020. Articles that examined the impact of cannabis use on youth with ADHD were included.

Results: Eleven studies were identified that compared outcomes for individuals with ADHD who used cannabis or synthetic cannabinoids against those with ADHD who did not. Seven of these studies used neuroimaging techniques, including fMRI, structural MRI, and SPECT. Differential regions of activation were identified, including the right hippocampus and cerebellar vermis, and bilateral temporal lobes. Morphological differences were identified in the right precentral and postcentral gyri, left nucleus accumbens, right superior frontal and postcentral gyri. No study identified any additive or ADHD × cannabis use interaction on neuropsychological tasks of executive function. Two studies found adverse differential impacts of early-onset cannabis use in this population.

Conclusion: A dearth of evidence is available on the impact of cannabis use on the developing brain and functioning for individuals with ADHD, despite the elevated risk for substance use in this population. The limited, potentially underpowered evidence does not support the hypothesis that cannabis use has a deleterious impact on neuropsychological tasks in transitional age youth with ADHD. Larger and longer-term studies are needed, however, to better inform clinicians and patients as to the impacts of cannabis use in youth with ADHD.

Keywords

ADHD; cannabis; neurodevelopment; systematic review

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a common disorder of persistent inattention, or hyperactivity/impulsivity that interferes with development; its worldwide prevalence is between 5% and 10%.[1,2] Although there is variability across studied populations, multiple studies suggest that a majority of individuals with ADHD meet diagnostic criteria for other psychiatric conditions, with learning disorders, oppositionality, substance use, and anxiety being particularly highly comorbid.[3,4] ADHD is linked to a number of negative developmental outcomes[5] and has a large societal burden because of both use of services and indirect factors such as impact on parent functioning.[6] The functional outcomes of youth with ADHD have been robustly studied, including findings of lower academic achievement,[7] peer problems, family conflict, and impairments in occupational performance.[8] These problems have a lasting impact on income[9] and life satisfaction.[10] While findings have been heterogeneous, impaired performance has been seen for children with ADHD across a number of neuropsychological domains, including but not limited to sustained attention, verbal and working memory, processing speed, response inhibition, reward processing, motivation, cognitive control, and impulsivity,[11–14] as well as modest adverse effects on IQ in adolescence (though a potential independent effect of ADHD on IQ is controversial).[15] Imaging studies have also shown numerous differences in neurodevelopment, spanning alterations in structural brain morphology[16,17] and differences in activation patterns in attentional networks, and in executive functioning, spanning a range of task and resting-state paradigms, including hypoactivation in bilateral frontal, right parietal, right temporal, and bilateral putamen.[18–20] Studies of cognitive control have implicated the importance of maturation of frontostriatal and anterior cingulate gyrus circuity, and have shown impairment in children with ADHD.[19] Children with ADHD also have smaller surface area in frontal, temporal, and cingulate regions, as well as thinner temporal pole and fusiform gyrus.[21]

Cannabis use is particularly prevalent in adolescents with ADHD: 38% of participants in a large multisite study of adolescent cannabis users met diagnostic criteria for ADHD.[22] Extensive research has linked ADHD as an independent risk factor to cannabis use.[23,24] ADHD may predispose individuals to earlier onset of cannabis use compared to their peers,[25] with additional evidence suggesting that increased ADHD symptomatology is associated with earlier initiation of use.[26] Increased ADHD symptom burden may also lead to heavier ongoing cannabis use.[27,28] Apart from earlier initiation, the trajectories of cannabis use for individuals with ADHD may also be different. Specifically, while individuals without childhood ADHD who abuse cannabis and alcohol in adolescence demonstrate developmentally appropriate decreases in substance use in early adulthood, individuals with childhood ADHD demonstrate persistent patterns of increased use into adulthood.[29] Of particular concern, youth diagnosed with ADHD are (statistically) significantly more likely than their peers to progress toward a substance use disorder (SUD) diagnosis.[30] Notably, however, appropriate treatment of ADHD may be associated with reduced risk of negative SUD outcomes.[31]

Cannabis use alone has known effects on neurodevelopment and cognition in adolescents across many of the same domains as ADHD. Increasing levels of adolescent cannabis use

have been correlated with lower levels of degree attainment, income, and life satisfaction.[32] Regular cannabis use in adolescence has been associated with impaired sustained attention and verbal and working memory.[33,34] Adolescent cannabis use has been independently associated with poor attentional functioning at follow-up in young adulthood across multiple neuropsychological tests, including visual scanning and the Trail Making Test.[35,36] Evidence also suggests that cannabis use in adolescence may alter brain circuitry responsible for processing speed,[37] response inhibition,[38] reward processing,[39] motivation,[40] cognitive control,[41] and impulsivity.[42] Early-onset cannabis use, in particular (versus late onset), has been associated with lower total IQ,[43] with more persistent use associated with greater impairment.[44] In young-adult heavy cannabis users, gray matter volume in the hippocampus and amygdala is negatively correlated with the amount of cannabis use.[45] Cerebral blood flow has been observed to be reduced in several cortical regions in otherwise healthy adolescent cannabis users, including left superior and middle temporal gyri, left insula, left and right medial frontal gyri, and left supramarginal gyrus.[46] Some evidence suggests that adolescent cannabis users rely on different neural mechanisms than non–cannabis users to achieve similar task performance, referred to as a "compensatory mechanism."[47] Given the overlap of affected functional domains between ADHD and cannabis use, one may wonder about common neurobiological risk factors between the two diagnoses. Although the research in this area is limited, a recent genome-wide association study found a highly significant genetic correlation between ADHD and cannabis use.[48]

Despite the extensive evidence base for neurodevelopmental outcomes that independently exists for both cannabis use in adolescence and ADHD across many similar domains, little is known about the combined impact of comorbid cannabis use and ADHD in adolescence. Meta-analyses have found that childhood ADHD is highly related to the odds of both cannabis use and dependence; this finding is likely related, however—at least in part—to comorbid behavioral disorders such as oppositional defiant disorder or conduct disorder.[24] While the exact prevalence of co-occuring ADHD and cannabis use disorder in adolescence is unknown, roughly a quarter of adolescents with an SUD have comorbid ADHD,[49] and youth with ADHD are six times more likely than peers to have drug/alcohol abuse.[50] It is especially critical that we understand the neurodevelopmental impact of cannabis use on individuals with ADHD, given recent changes in regulation and in societal views on cannabis use. Both medical and recreational cannabis use is increasingly becoming legalized in a number of U.S. states, and preliminary research has shown a subsequent association with increasing rates of adolescent cannabis use following legalization.[51] On average, parental views on adolescent cannabis use are different than adolescent perspectives. Parents of children with chronic medical conditions (including ADHD) who were surveyed about the perceived risk of cannabis for their medically vulnerable child largely feel that it is risky for their child.[52] By contrast, high school seniors do not perceive cannabis to be particularly risky, with only 26.7% reporting use as harmful.[53] Similarly, adolescents with ADHD who use cannabis have often reported thinking that it would lead to improvement in their ADHD symptoms.[54] These observations are in line with globally increasing trends in adolescent cannabis use in the face of decreased use of other illicit substances.[55] Together with other factors, such as tetrahydrocannabinol (THC) potency roughly tripling from 1995 to 2014,[56] it is increasingly critical to establish the links between ADHD and cannabis use and their

shared impact on neurodevelopmental outcomes. An empirically based understanding of comorbidity between these conditions has several important implications, including early detection and treatment engagement, as well as development of focused interventions, such as modified motivational interviewing techniques or use of biomarkers to track treatment response.

To this end, we set out to systematically review the literature to determine what is known about the functional impact of cannabis use on youth with ADHD. This search broadly defined neurodevelopmental outcomes to include neuroimaging, neuropsychological testing, and questionnaire-based studies that captured the developmental or functional impacts of cannabis use on youth with ADHD.

METHODS

A systematic review of the literature was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (see Supplemental Table 1 for the PRISMA checklist, http://links.lww.com/HRP/A160). The review protocol was developed in advance and registered with the international prospective register of systematic reviews (PROSPERO no. 165360).

Four databases were queried for this search: PubMed, Embase, PsycINFO, and the Cochrane CENTRAL trials register. Our search was limited to articles published in English before 1 January 2020. The search strategy for these databases was the following:

- (ADHD OR “attention deficit” OR “attention deficit hyperactivity disorder” OR “attention-deficit/hyperactivity disorder”) AND
- (Cannabis OR marijuana) AND
- (Child OR adolescent OR teen OR pediatric OR “young adult” OR “transitional age” or “youth”)

In order to be included, studies needed to include participants who were adolescents or young adults (age <25), compare individuals with ADHD or subthreshold ADHD who used cannabis or synthetic cannabinoids to those who did not, and measure any neurodevelopmental outcome (defined broadly to include neuroimaging, symptoms, and functioning). We excluded editorials, review articles, conference abstracts, and consensus guidelines. After duplicates were removed, an initial assessment of every title and abstract was undertaken. Full-text articles were then independently assessed by two psychiatrists (PC and JL) against the inclusion and exclusion criteria, with a third psychiatrist (DH) serving as tiebreaker. Key data from each article were extracted and summarized into table format, including study population, methodology, and outcomes. Study authors of articles with missing data of interest were queried via email for additional information about group sizes and mean ages.

RESULTS

Our search strategy yielded a total of 1202 articles (765 after duplicates were removed). Supplemental Figure 1, http://links.lww.com/HRP/A161, shows our PRISMA flow diagram

and the process that ultimately yielded 11 articles for inclusion in this review. No additional articles were identified outside of the systematic review. Seven of these included studies used neuroimaging to examine outcomes; two focused on neuropsychological tests; and two were primarily questionnaire based. Ten articles involved participants diagnosed with ADHD, and one article included individuals with subthreshold ADHD. One article recruited adolescents solely with synthetic cannabinoid use, and the other ten recruited cannabis users. The participants, measures, and outcomes of each study are outlined in Table 1.

Functional MRI Studies

Three studies (Rasmussen and colleagues,[57] Newman and colleagues,[58] and Kelly and colleagues[59]) enrolled subjects from longitudinal follow-up of the Multimodal Treatment Study of ADHD (MTA study)[60] and used functional magnetic resonance imaging (fMRI) to investigate the impact of cannabis use on youth with ADHD.

Rasmussen and colleagues[57] used the go/no-go paradigm to examine response inhibition while transitional age youth (age 21–27) underwent fMRI scanning. They compared young adults with childhood ADHD with and without at least monthly cannabis use over the past year (n = 25 in each group) with a control group with (n = 11) and without (n = 12) cannabis use. There were differences in both task performance (significantly more commission errors in ADHD groups) and fMRI activity (less frontoparietal and frontostriatal activity in ADHD groups) for ADHD versus control groups. However, there were no main effects of cannabis use on response inhibition or functional brain activation. One notable finding was an interaction effect between ADHD diagnosis and cannabis use. The authors found increased recruitment in the right hippocampus and cerebellar vermis in cannabis-using controls during correct response inhibition; by contrast, individuals with ADHD who also used cannabis had lower activation in these regions for response inhibition. The study authors hypothesize that this finding may have reflected a compensatory strategy in cannabis-using controls but not ADHD participants—which they speculate may be due to generally delayed maturation of the frontocerebellar and fronto-striatal-thalamic networks in the ADHD group.

In a similar study, Newman and colleagues[58] examined go/no-go task performance while individuals underwent fMRI scanning. Subjects again were prior MTA study participants, now young adults (mean age = 24.6) with childhood ADHD diagnoses (53 of 78 had persistent ADHD diagnosis in young adulthood) with and without cannabis use in the last year compared to 36 controls without ADHD diagnoses (20 of whom were cannabis users). Those with persistent ADHD had the highest commission error rate, followed by those with childhood ADHD diagnoses that remitted by adulthood, with the lowest error rate in the control group. This study found that poor task performance was associated with thicker caudal inferior frontal gyrus; this effect was not mediated by either ADHD status or cannabis use.

Kelly and colleagues[59] recruited subjects (ages 21–25) from the MTA study, 14–16 years after MTA baseline, and used fMRI to study alterations in brain functional organization. They compared performance on five indices of executive functioning (motor response inhibition, cognitive interference, processing speed, risky decision making, and delayed

recall) in a 2 × 2 design, crossing ADHD diagnosis and cannabis use. A total of 45 individuals with ADHD (23 with weekly cannabis use) were compared to 30 control subjects (15 with weekly cannabis use). While the authors found weaker intrinsic functional connectivity in executive functioning and somatomotor networks for individuals with ADHD, they found no interaction effects with cannabis use. In fact, cannabis use–related alterations in intrinsic functional connectivity were suggestive of neuroadaptation in non-overlapping networks, including the default mode and lateral visual networks, irrespective of ADHD diagnosis. The study authors concluded that cannabis use does not exacerbate underlying vulnerabilities in individuals with a childhood diagnosis of ADHD.

Structural MRI Studies

Two studies used structural MRI as their primary methodological tool. The first, by Lisdahl and colleagues,[61] also recruited subjects from longitudinal follow-up of the MTA study. They compared 81 individuals with a childhood ADHD diagnosis (37 cannabis users, defined as at least monthly use over the last year) to 39 controls (18 cannabis users) and found that cannabis use was independently associated with decreased cortical thickness in the right hemisphere superior frontal sulcus, anterior cingulate, and isthmus of cingulate gyrus regions, and in the left hemisphere superior frontal sulcus and precentral gyrus regions, whereas childhood ADHD diagnosis was not associated with any differences in brain morphology. When looking at the interaction between diagnosis and substance use, authors found that early cannabis use (age 16 or younger) in individuals with ADHD was associated with significantly thicker right superior frontal and postcentral gyri and with larger left nucleus accumbens compared to later onset of cannabis use.

Çolak and colleagues[62] examined the impact of synthetic cannabinoids on brain structure. Synthetic cannabinoids are compounds that imitate the effects of Δ-9-THC on cannabinoid receptors but are full agonists—unlike THC, which is a partial agonist. The researchers recruited 28 synthetic cannabinoid users (13 with ADHD) and compared them to 13 controls, all between the ages of 14 and 18. Inclusion criteria included synthetic cannabinoid use at least three times a week over preceding six months. Adolescents who had an ADHD diagnosis and used synthetic cannabinoids were found to have decreased cortical thickness in the right precentral and postcentral gyri. Volume was also increased in the right nucleus accumbens in synthetic cannabinoid users without ADHD, but not with ADHD, compared to controls.

Single-Photon Emission Computer Tomography Studies

Two studies used single-photon emission computer tomography as their primary imaging modality. Amen and Waugh[63] imaged young adults (mean age = 28) with ADHD as determined by structured diagnostic interviews, with one group (n = 30) who used cannabis at least weekly for the prior year and one who did not (n = 10; notably, there was no control group without ADHD). Both groups showed prefrontal cortex hypoperfusion. Unique to the cannabis-using group was bilateral temporal lobe hypoperfusion.

Silva and colleagues[64] examined a treatment-naive cohort of Brazilian adolescents (ages 15–21) where the substance use group included both cannabis (18 of 18) and cocaine (6 of

18 subjects) use. To meet inclusion criteria, subjects had to meet *Diagnostic and Statistical Manual of Mental Disorders* (DSM)–IV criteria for substance abuse/dependence, with no formal frequency/duration-of-use requirement (use was quite frequent: the mean frequency of cannabis use was 28 days in last month for the ADHD/SUD group, and 24 days in the SUD-alone group). The investigators measured striatal dopamine transporter density and found that in both the right and left striatum, the highest dopamine binding potential was in the ADHD group, followed by the ADHD + SUD group, then healthy controls, and then SUD alone.

Neuropsychological Testing Studies Without Neuroimaging

We identified two studies that used extensive neuropsychological testing batteries to understand the impact of cannabis use. Tamm and colleagues[65] recruited 87 patients (42 who self-reported monthly or more frequent cannabis use during the previous year) from the MTA study and 41 controls (20 with cannabis use), and assessed various measures of executive functioning. For nearly every task, ADHD diagnosis had a deleterious effect on performance, but cannabis use did not. The authors did not observe any significant interactions between diagnosis and cannabis use. With exploratory analysis, the authors did find that earlier use of cannabis (initiation before age 16: n = 27) was associated with poorer performance on cognitive tasks assessing decision making, working memory, impulsive errors, and response variability than later onset of use (age 16 or later: n = 32).

Wallace and colleagues[66] examined young adults with subclinical ADHD symptoms, rather than those diagnosed with ADHD. They compared 34 weekly cannabis users (required three weeks of abstinence prior to neuropsychologic testing) to 38 controls, and found that cannabis use resulted in impaired sustained attention but did not find an ADHD × cannabis-use interaction. Subclinical ADHD symptoms did not result in worse task performance on any measures.

Questionnaire-Based Studies

The final two studies meeting inclusion criteria did not rely on neuroimaging or neuropsychological testing but, instead, on patient self-report. Hollis and colleagues[67] sought to compare mental health functioning (a composite index derived from the Schizotypal Personality Questionnaire, Strengths and Difficulties Questionnaire, and Global Assessment of Function) between users and nonusers of cannabis for three groups: ADHD, genetic high risk for schizophrenia, and healthy controls. Subjects were between 14 and 21 years old and included 25 individuals with ADHD (9 of whom were cannabis users). Negative impacts of cannabis were seen only in the group at high risk for schizophrenia.

Finally, Ly and Gehricke[68] queried a group of 76 young adults (mean age = 26) with ADHD about their cannabis use, ADHD symptoms, and sleep quality. There was no control group of individuals without ADHD. These researchers found significant differences by sex, wherein higher rates of cannabis use were associated with more inattentive symptoms in males, while higher rates of cannabis use in females were associated with decreased sleep quality.

DISCUSSION

In this systematic review we identified just 11 published studies that examined the impact of cannabis use on neurodevelopment in youth with ADHD. Perhaps surprisingly, as cannabis use demonstrates clear and consistent adverse effects on cognition as measured by neuropsychological task performance, no study identified a significant differential impact of cannabis use on these measures for individuals with ADHD compared to nonusers. Differential impacts were seen, however, with regard to brain morphology (including decreased thickness in the right precentral and postcentral gyri,[62] and increased thickness in the left nucleus accumbens and right superior frontal and postcentral gyri[61]) as well as dopamine transporter density differences (lower dopamine transporter availability in individuals with combined ADHD and SUD[64]). The functional impact of these differences remains to be seen, as cannabis use in individuals with ADHD has not, to this point, been demonstrated to be associated with impaired task performance. It is entirely possible that some of these functional alterations represent a compensatory mechanism enabling satisfactory task performance, or it may be that the tasks are not able to capture specific deficits, limiting our ability to draw firm conclusions. To the extent that conclusions can be drawn from these studies, there is support[59,65] for Rasmussen's comment that "the neurodevelopmental effect of an ADHD history appears to exert a markedly more pronounced effect on behavioral and brain signatures of impulsivity than cannabis exposure."[57] While impairment in neurodevelopmental outcomes due to cannabis in individuals with ADHD has not been demonstrated to date, other research that has found cannabis exposure correlated with deleterious impacts on healthy brain development;[69] these results should therefore not be interpreted as providing strong evidence of a lack of effect.

Limitations

Multiple limitations need to be considered prior to establishing a definitive statement regarding interaction effects between ADHD status and cannabis exposure. The sample sizes of all included articles were modest at best. The largest sample of individuals with ADHD was just 87, and discussions of statistical powering were limited, leaving us to wonder whether the studies were sufficiently powered to detect differences on task performance with smaller effect sizes. Further, the MTA study population was potentially oversampled, as 5 of 11 studies (including all 3 fMRI studies) recruited patients from long-term follow-up of the MTA study, presumably reducing the number of unique individuals studied overall and predisposing to potential sampling bias. Additionally, many of these studies had strict exclusionary criteria, such as no additional comorbid psychiatric diagnoses or use of psychotropic medications. Males also significantly outnumbered female subjects. Broader selection of cohorts for replication of these findings would be indicated to determine whether the patterns identified are generalizable. Additionally, medication treatment among study participants with ADHD varied widely, with very low rates of medication use in the studies that recruited from MTA. Although medication washout prior to testing was the norm when specified, it is an open question how adherence to long-term treatment may affect results, especially given a lack of high-quality studies on the impact of long-term stimulant use.[70]

Inclusion of studies—In this review, one of the 11 included studies involved adolescents and young adults with *subthreshold* ADHD. While this population may differ from those diagnosed with ADHD, we felt it relevant to include given the quality of the study and the conceptualization of ADHD as a spectrum illness.[71] In the same vein, we included one article that studied synthetic cannabinoid use—although synthetic cannabinoids are full agonists of cannabinoid receptors rather than partial agonists like cannabis—given that the high-quality study included younger participants (ages 14–18) and that differences in potency are currently poorly controlled across all included studies.

Measures and patterns of cannabis use—Most of these studies measured substance use by self-report without laboratory confirmation. There are also limitations with the operationalization of "cannabis use" across the identified studies. Definitions of use spanned from monthly to multiple times a week, and differences in potency were not addressed (which may lead to significant variability when comparing older studies to more contemporary ones, given the known increase in THC potency). Addiction medicine research indicates that differences in quantification of cannabis use across studies (including limited measurements about quantity consumed on a typical day, duration of inhalation, THC potency) has been a major limitation to understanding the adverse consequences of cannabis use.[72] By contrast, the majority of these studies used well-validated measures to ensure the accuracy of the ADHD diagnosis, such as the Diagnostic Interview Schedule for Children (DISC) or Structured Clinical Interview for DSM (SCID).

Patterns of use are particularly relevant when considering potentially important findings seen across two studies[61,65] that identified *early* cannabis use as differentially predictive of negative outcomes. In the Tamm and colleagues study,[65] early cannabis use (prior to age 16) was associated with poor performance on a variety of cognitive tasks (response inhibition, decision making, cognitive control), and in the Lisdahl and colleagues study,[61] with structural MRI differences (larger left nucleus accumbens and thicker right superior frontal and postcentral gyri). These age-related questions represent an important area for future study, especially as evidence is beginning to mount that early cannabis use is associated with worse mental health outcomes, including greater symptoms of depression and anxiety.[73]

Excluded studies—Although a small number of articles did not meet our inclusion criteria because they did not measure neurodevelopmental or functional outcomes, they are nonetheless important to understanding the role of cannabis use in the development of individuals with ADHD. Patel and colleagues[74] used a large community hospital database to compare the hospitalizations of over 10,000 adolescents with ADHD. They found that co-occurring cannabis use disorder was associated with increased inpatient cost, longer inpatient stay, and higher comorbidity of alcohol abuse. Merrill and colleagues[75] conducted a latent profile analysis using data from the Pittsburgh ADHD Longitudinal Study and found that about 10% of the sample fit a "high marijuana use group." Individuals in this group had impairment in peer relationships, educational attainment, and financial dependence compared to non-ADHD controls who used some cannabis. Finally, a mixed qualitative-quantitative study by Mitchell and colleagues[76] using participants from the MTA follow-up

identified two major themes, especially among persistent ADHD users: these individuals felt that cannabis reduces negative moods and that it positively affects ADHD symptoms. This subjective sense that cannabis use improves ADHD symptoms further supports the urgent need for more definitive neuropsychological studies. It is difficult to postulate a mechanism by which the impairments found in youth with cannabis use somehow compensate for the impairments in the same domains found in youth with ADHD.

Conclusion

In conclusion, there is currently a limited base of evidence regarding the impact of comorbid cannabis use in adolescents and young adults with ADHD. Preliminary evidence suggests altered brain morphology and dopamine transporter density, along with perfusion abnormalities. Future research must also determine whether any such differences are associated with differential neuropsychological task performance. ADHD diagnosis is clearly associated with worsened executive function, but the evidence to date does not clearly support either an addictive effect or an interaction—whether protective or harmful—with cannabis use. These conclusions should be viewed with caution as the current evidence base is quite limited; larger studies are needed. The increasing use and availability of cannabis associated with legalization, as well as the increasing potency of cannabis formulations, are important clinical and societal reasons to understand the neurodevelopmental effects of cannabis use, particularly in groups such as young people with ADHD, who might be particularly vulnerable to such effects. Even *additive* effects on neurodevelopmental measures in persons with preexisting neurocognitive impairment or risk for such would be expected to add substantially to functional impairment and may increase the number of youth who cross important thresholds such as not graduating from high school or being involved in a motor vehicle accident.

This review highlights the urgent need for ongoing research into the suspected neurodevelopmental alterations resulting from comorbid cannabis use by youth with ADHD. The Adolescent Brain Cognitive Development Study[77] is an ongoing, large (over 10,000 youth recruited), multisite, national, longitudinal study that aims to follow 9–10-year-olds for ten years and includes detailed measures of substance use[78,79] as well as brain imaging and measures of neurocognition. Rather than cross-sectional snapshots in time, this framework should yield a better understanding of developmental trajectories, progression of mental health disorders, and intersection between societal changes (e.g., less restrictive cannabis laws) and outcomes. We anticipate this important study may begin to provide answers to some of the questions that this article has shown to be unanswered—including understanding whether cannabis does actually alter neural circuitry in youth with ADHD, how this affects task performance, and perhaps most critically, the longer-term functional outcomes for adolescents with ADHD who use cannabis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Summary of Studies Examining Impact of Cannabis Use on Youth with ADHD

Study	Number of participants by group (mean age)	Number of female participants (%)	Methodology	ADHD diagnosis & cannabis instruments (minimum cannabis use frequency for study inclusion)	Number of participants with active ADHD medication treatment	Findings related to cannabis use in ADHD population
Functional MRI						
Rasmussen et al. (2016)[57]	MTA: 25 ADHD+ C+ (24.6) 25 ADHD+ C− (25) 11 ADHD− C+ (24.2) 12 ADHD− C− (24.1)	16/73 (22%)	fMRI with go/no-go task	DISC Substance Use Questionnaire (at least monthly)	2/25 ADHD+ C+ 0/25 ADHD+ C− 24-hour medication abstinence prior to testing	No main effects of cannabis use on response inhibition task performance or functional brain activation An interaction of diagnosis × cannabis was found in right hippocampus and cerebellar vermis during successful response inhibition in cannabis using controls
Newman et al. (2016)[58]	MTA: 78 ADHD+ (24.8) 19 ADHD− C+ (24.1) 17 ADHD− C− (24.2)	20/114 (18%)	fMRI with go/no-go task	DISC Substance Use Questionnaire (at least yearly)	6/78 ADHD+	Poorer go/no-go task performance was associated with thicker caudal inferior frontal gyrus This effect was not mediated by ADHD status or history of substance use
Kelly et al. (2017)[59]	MTA: 23 ADHD+ C+ (24.7) 22 ADHD+ C− (25.3) 15 ADHD− C+ (24.5) 15 ADHD− C− (24.4)	14/75 (19%)	fMRI with neuropsychiatry battery: Go/no-go task D-KEFS-CWI Trail Making Test-Part B Iowa Gambling Task Hopkins Verbal Learning Task	DISC Substance Use Questionnaire Substance Use Recency Questionnaire (at least weekly)	1/23 ADHD+ C+ 2/22 ADHD+ C− 24-hour medication abstinence prior to testing	No cannabis use × ADHD diagnosis interactions were observed on any task Weekly cannabis use did not exacerbate underlying neuronal vulnerabilities in individuals with a childhood diagnosis of ADHD
Structural MRI						
Lisdahl et al. (2016)[61]	MTA: 37 ADHD+ C+ (24.3) 44 ADHD+ C− (24.6) 18 ADHD− C+ (23.6) 21 ADHD− C− (23.4)	22/120 (18%)	Structural MRI	DISC Substance Use Questionnaire Substance Use Recency Questionnaire (at least monthly)	4/37 ADHD+ C+ 2/44 ADHD+ C− 24-hour medication abstinence prior to testing	Early cannabis use (age 16 and younger), compared to later use onset, in individuals with ADHD was associated with larger left nucleus accumbens and thicker right superior frontal and postcentral gyri
Çolak et al. (2019)[62]	13 ADHD+ C+ (16.0) 15 ADHD− C+ (15.9) 13 ADHD− C− (16.5)	0/41 (0%)	Structural MRI	KSADS (present and lifetime versions) Self-report (at least 3 times weekly)	Study excluded individuals who used psychoactive medications over preceding two months	Synthetic cannabinoid users with ADHD showed decreased cortical thickness in the right precentral and postcentral gyri compared to controls This finding was not seen when comparing synthetic cannabinoid users without ADHD to controls
Single-photon emission computer tomography						

Study	Number of participants by group (mean age)	Number of female participants (%)	Methodology	ADHD diagnosis & cannabis instruments (minimum cannabis use frequency for study inclusion)	Number of participants with active ADHD medication treatment	Findings related to cannabis use in ADHD population
Amen & Waugh (1998)[63]	30 ADHD+ C+ (28) 10 ADHD+ C− (30)	11/40 (28%)	SPECT with Conners Continuous Performance Test	Clinical Interview Self-report (at least weekly)	One-week stimulant medication washout prior to imaging	Individuals with ADHD who used cannabis demonstrated bilateral temporal lobe hypoperfusion compared to those with ADHD who did not use cannabis
Silva et al. (2014)[64]	18 ADHD+ C+ (17.5) 11 ADHD+C− (16.1) 14 ADHD− C+ (18.3) 19 ADHD− C− (17.7)	0/62 (0%)	SPECT with radioligand to evaluate dopamine transporter density in the striatum	KSADS-Epidemiological version International Neuropsychiatric Interview with urine drug screen confirmation	All participants were treatment naive	The comorbidity of ADHD with SUD (cannabis and cocaine) in adolescents was associated with lower dopamine transporter availability
Neuropsychological battery without neuroimaging						
Tamm et al. (2013)[65]	MTA 42 ADHD+ C+ (24.4) 45 ADHD+ C− (24.6) 20 ADHD− C+ (23.7) 21 ADHD− C− (23.4)	25/128 (20%)	Hopkins Verbal Learning Task Go/no-go task Iowa Gambling Task DKEFS-CWI Paced Auditory Serial Addition Test Trail-making task	DISC Self-Report on Substance Use Questionnaire (at least monthly)	4/42 ADHD+ C+ 2/45 ADHD+ C− 24-hour abstinence prior to testing	For nearly every executive function task, ADHD, but not cannabis, had a clear effect No significant diagnosis × cannabis use interactions were found
Wallace et al. (2019)[66]	34 C+ (21.9) 38 C− (20.7) Subjects had subthreshold ADHD diagnosis.	34/72 (47%)	Ruff 2&7 Conners Continuous Performance Test-II WAIS III Letter Number Sequencing DKEFS-CWI	Child Behavior Checklist Customary drinking and drug use record with toxicology screen confirmation (weekly use)	ADHD medication treatment was exclusionary	Cannabis use was associated with slower response on attention task but did not predict any of the other cognitive variables The ADHD × cannabis use interaction did not have significant impacts on attention
Questionnaires						
Hollis et al. (2008)[67]	9 ADHD+ C+ (16.7) 18 ADHD+ C− (15.8) 19 ADHD− C+ (18.6) 53 ADHD− C− (17.2)	44/99 (44%)	Schizotypal personality questionnaire Strengths and difficulties questionnaire Global Assessment of Function	Parental account of childhood symptoms Schedules for Clinical Assessment in Neuropsychiatry (more than once or twice)	27/27 ADHD+	No significant impact of cannabis use on individuals with ADHD on any measures
Ly & Gehricke, (2013)[68]	29 ADHD+ C+ (24.7) 47 ADHD+ C− (27.9)	20/76 (26%)	Assessment of hyperactivity and attention Pittsburgh Sleep Quality Index	Structural Clinical Interview for DSM disorders Self-report (at least every other month)	Not reported	Male subjects with higher rates of cannabis use showed significant correlation with number of inattentive symptoms Female subjects with higher rates of cannabis use saw correlations with decreased sleep quality

ADHD+, ADHD diagnosis; ADHD−, no ADHD diagnosis; C+, cannabis users; C−, cannabis nonusers; DISC (Diagnostic Interview Schedule for Children-Parent Report; DKEFS-CWI, Delis-Kaplan Executive Function System Color Word Interference Task; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; KSADS, Kiddie Schedule for Affective Disorders and Schizophrenia; MRI,

magnetic resonance imaging; MTA, subjects recruited from the Multimodal Treatment Study of ADHD; SPECT, single-photon emission computerized tomography; SUD, substance use disorder; WAIS, Wechsler Adult Intelligence Scale